THE ROLE OF DEPRESSION IN HEALTHCARE SERVICE UTILIZATION AND OPIOID AGONIST TREATMENT AMONG PERSONS WITH CO-OCCURRING OPIOID USE AND DEPRESSIVE DISORDERS

by
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Abstract

Background: Depression is the most common co-occurring mental health disorder among persons with opioid use disorder (OUD). Psychiatric comorbidity can impact healthcare utilization, particularly emergency department visits and hospitalizations, as well as continuity of treatment for opioid use disorder. The objectives of this dissertation are to enhance understanding of characteristics and health conditions among persons with co-occurring OUD and depression, and to explore the role depression plays in healthcare utilization and continuity of buprenorphine treatment.

Methods: Data were obtained from the Geisinger Health System (GHS), and included electronic health records for all healthcare encounters that occurred at any of the GHS facilities before the fall of 2019. In addition to electronic health records, ordered and dispensed prescription records were used. Adults 18 years old or older included in each of the study samples were recruited from one of Geisinger's outpatient addiction treatment clinics and all had at least one recorded OUD diagnosis in their electronic health record. Differences in characteristics and other diagnoses between persons with and without depression were assessed by multivariable logistic regression. Propensity score weighted Cox regression survival analysis for recurrent events was used to assess the association between OUD with prior depression and healthcare utilization. Propensity score weighted logistic regression was used to estimate odds of 180-day retention and any treatment discontinuation, and propensity score weighted Cox proportional hazards regression was implemented to estimate the hazard of treatment gaps or discontinuation for those with and without prior depression.

Results: Forty-nine percent of adults with OUD had a lifetime depression diagnosis. Persons with co-occurring depression were more likely to be female and have other common medical conditions, as well as other mental health and substance use disorders, and/or at least one overdose or suicide attempt or ideation. Compared to OUD without prior depression, OUD with prior depression was associated with increased risk of emergency department visits that included a substance use disorder, suicidal ideation or suicide attempt and/or mental health disorder code. Any prior or past year depression was associated with increased risk of treatment gap and/or discontinuation and past year depression was associated with decreased odds of 180-day buprenorphine treatment retention.

Conclusions: This dissertation highlights the complex healthcare needs of persons with co-occurring opioid use and depressive disorders, and the particular importance of the integration of depression care into medical care and treatment for opioid use disorder.

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Chapter 1: Introduction

1.1 Opioid overdose and opioid use disorder in the United States

Between the years of 1999 and 2018, over 750,000 people died from a drug overdose in the United States, and 69.5% of the drug overdoses in the 2018 involved an opioid.[1] This represents a 200% increase in the rate of opioid overdose deaths since 2000.[2] Today, overdose remains the leading cause of injury death in the United States.[3] In addition to mortality, opioid-related morbidity has increased substantially. The rate of inpatient hospitalization related to opioid misuse has increased over 150% since the 1990s[4] and the rate of opioid-related emergency department visits has increased by 99% since 2005.[5] While we have observed this increase in fatal and non-fatal overdose due to opioids, differing trends in the use of types of opioids exist. In the early 2000s, most opioid-related deaths were due to prescription opioids. Between 2000 and 2014, prescription opioid death rates increased from 1.5 to 5.9 deaths per 100,000 persons.[6] Opioid prescribing rates were also increasing during this time with 72.4 prescriptions per 100 persons in 2006 to 81.2 prescriptions per 100 persons in 2010. Although opioid prescribing rates have decreased in recent years, the prescription rate remains high when compared to rates from the late 1990s.[7] Over the past 10 years, the use of heroin and deaths due to heroin overdose have increased substantially. From 2000 to 2013 rates of heroin overdose death quadrupled and continued to increase.[8] In 2017, almost 500,000 adults reported using heroin in the past year and the heroin overdose death rate was 5 per 100,000 adults in the US.[9,10] Most recently, there has been a surge in deaths due to fentanyl and other synthetic opioids (other than methadone); the number of deaths increased approximately 45% from 2016 to 2017.[9]

In 2018, 10.3 million people 12 years old or older reported using opioids in a way not directed by a health provider.[11] Among these 10.3 million adults, 9.9 million (97.1%) reported using prescription opioids and 808,000 (7.9%) reported any heroin use in the past year. Two

million people at least 12 years old in the US had an opioid use disorder (OUD), including heroin and/or prescription opioids, in 2018. This percentage is similar to that of 2016 and 2017, but lower than the proportion of adults with an opioid use disorder in 2015.[11] Opioid use disorder is defined by the DSM-5, as problematic pattern of opioid use that leads to clinically significant impairment and/or distress. A number of criteria are used to diagnose an opioid use disorder. These criteria fall into four groups, including impaired control (e.g. craving), social impairment (e.g. reduction in other social, occupational or recreational activities due to opioid use), risky drug use (e.g. putting oneself in harm), and physiological problems (e.g. tolerance and withdrawal).[12]

1.2 Substance use and mental health comorbidity: opioid use disorder and depression

Substance use disorders are more prevalent among adults with mental health disorders compared to adults without mental health disorders.[13] In 2018, 9.2 million adults in the US had co-occurring past-year mental health and substance use disorders, corresponding to 3.7% of adults in the US.[11] Further, among adults with a substance use disorder, 47.7% had a past-year mental health disorder.[11] Among persons with opioid use disorder, 64.3% had any mental illness in the past year and 26.7% had a serious mental illness according to the 2015-2017 National Survey on Drug Use and Health.[14]

Major depressive disorder is among the most common mental illnesses that co-occur with opioid use disorder. In studies using US national survey data, lifetime prevalence of co-occurring OUD and major depressive disorder (MDD) among individuals with OUD has been shown to be as high as 50-60%.[15,16] Among treatment seeking or enrolled populations, current prevalence of MDD is 27% among persons in treatment for non-medical prescription opioid use[17] and 19.4% among patients receiving buprenorphine/naloxone treatment.[18]

Mental health disorder comorbidity is associated with lower reported quality of life and an increase in severity of mental health and substance use symptoms.[19,20] Further, persons with co-occurring substance use and mental health disorders face increased barriers to accessing treatment, and experience challenges with substance use treatment completion.[21–23] Particularly with opioid use disorder and depression, comorbid depression is associated with increased risk of opioid misuse, overdose and suicide.[21,24–28]

Co-occurring mental illness also impacts healthcare service utilization including increased emergency department use among persons with substance use disorders.[29,30] Among individuals with OUD, the increased use of emergency department services is potentially linked to unmet need for treatment of depression.[31]

1.3 Opioid agonist treatment for opioid use disorder

The use of opioid agonist medications is considered to be the standard of care for OUD.[32] Two types of opioid agonist medications are used to treat opioid use disorder- methadone and buprenorphine. Methadone, a full agonist, activates opioid receptors and works to reduce opioid cravings and withdrawal symptoms.[33] Methadone is taken orally once per day and is typically dispensed through Opioid Treatment Programs (OTPs). Methadone has been used since the 1960s; approximately 21-25% of clients at substance use treatment facilities with OTPs receive methadone each year.[34] Buprenorphine is a partial opioid agonist at the mu receptor and an antagonist at the kappa receptor. Like methadone, buprenorphine reduces craving and withdrawal symptoms and does not produce euphoria.[33] Buprenorphine was approved as a treatment for opioid use disorder by the Food and Drug Administration in 2002 (tablet-form) and is dispensed by medical providers who have a waiver to prescribe buprenorphine.[34] Non-extended release buprenorphine can be taken orally or sublingually and typically taken once or

twice daily.[33] The percentage of substance use outpatient treatment facilities in the US that offer medication-based treatment for opioid use disorder increased from 20% in 2007 to 36.1% in 2016.[35] A larger increase was found for buprenorphine with 14.9% of facilities in 2007 to 25.4% in 2016, compared to methadone which was offered at 9.4% of treatment facilities in 2007 and 10.3% in 2016. This same study found that in 2016, only 6.1% of facilities offered all three approved medications (methadone, buprenorphine and naltrexone) to treat opioid use disorder.[35] Another study that assessed information about healthcare providers waivered to prescribe buprenorphine found the prevalence of waivered prescribers increased from 3.8 to 17.3 per 100,000 persons in 2017. However, this corresponds to less than 10% of all primary care providers in the US.[36]

Opioid agonist treatment (OAT) is associated with increased treatment retention and a decrease in the use of opioids as well as other adverse effects of OUD including overdose deaths, criminal justice involvement, and transmission of HIV and Hepatitis C.[27,37–41] Despite evidence supporting the use of OAT, a small proportion of adults with OUD receive OAT[42,43] and among those who do receive it, a number of challenges exist including low adherence and treatment retention rates, as well as inadequate dosing and stigma associated with OAT.[33,44–46]

1.4 Depression and opioid agonist treatment

Psychiatric comorbidities are a known contributor to reduced access to substance use disorder treatment, lower retention and poorer outcomes among adults with substance use problems.[20–23,47] However, research on the effects of psychiatric comorbidity on OAT does not necessarily align with the broader relationship between psychiatric comorbidity and substance use treatment. Existing studies have found no significant relationship between psychiatric comorbidity and early discontinuation of buprenorphine treatment.[48,49] Another found no

association between psychiatric comorbidity and methadone or buprenorphine non-completion and weak association with time to attrition regardless of the type of opioid for which a client was admitted for.[22] Others show a positive association, with psychiatric comorbidity associated with greater odds of continuous buprenorphine treatment for at least one year[50] and a decreased likelihood of opioid use at 12 weeks of buprenorphine treatment; however this difference was not observed at 24 weeks.[51]

Existing evidence on the association between depression and OAT is also not entirely consistent.[52] Some studies have found positive treatment outcomes associated with depression. For example, Gerra and colleagues found that patients who remained in buprenorphine treatment at 12 weeks compared to those who dropped out had a higher rate of depression at baseline.[53] Dreifuss and colleagues assessed the impact of pre-treatment characteristics on buprenorphine/naltrexone treatment and found that lifetime depression was associated with prescription opioid abstinence at week 12 of treatment.[54] Although a secondary analysis using data from the same randomized controlled trial did not find an association between reduction of depression symptoms during treatment and opioid abstinence at the 12 week follow-up.[55] Another study found no significant association between depression and buprenorphine treatment outcomes.[56] Additionally, among those with co-occurring depression who also received antidepressant treatment, there was no clear difference in OAT drop-out or drug use among those receiving antidepressant medications and those receiving placebo.[57] The association between depression and buprenorphine continuity is complex and likely differs from other mental health disorders because of antidepressant effects of buprenorphine.[58,59] However, limitations of existing studies include grouping depression into overall psychiatric comorbidity and short length of treatment follow-up.

1.5 Overdose risk: role of opioid agonist treatment and co-occurring depression

Opioid agonist treatment is associated with a reduction in risk of overdose mortality among individuals with OUD.[40,41,60] Risk of overdose mortality is highest immediately following cessation of treatment.[40] Periods in methadone or buprenorphine treatment are associated with reduced hazard of opioid overdose compared to periods in treatment that do not involve medications. However, compared to periods in non-medication treatment, periods after discharge from methadone or buprenorphine treatment have similar risk of overdose indicating the importance of treatment retention.[60] In addition, mental health hospital admissions and admissions related to self-harm are associated with increased risk of fatal opioid overdose following OAT.[61] Further, depression is a risk factor of overdose, as well as suicide.[24,28] According to the National Survey on Drug Use and Health, people who use opioids regularly were 75% more likely to create a plan for suicide and two times as likely to attempt suicide compared to those who did not report using opioids.[28] It is also estimated that 21-33% of overdose deaths are intentional.[28,62,63] These findings highlight the need to understand the role of depression in continuity of opioid agonist treatment, which may in turn highlight ways to mitigate both risk of overdose and intentional self-harm among persons with co-occurring opioid use disorder and depression.

1.6 Opioid epidemic in Pennsylvania

Pennsylvania, where data for this dissertation comes from, is among the states with the highest rates of overdose deaths, with an age-adjusted drug overdose death rate of 36.1 per 100,000 compared to the national rate of 20.7 in 2018.[64] Sixty-five percent of drug overdose deaths in Pennsylvania involved an opioid in 2018.[65] Between the years of 1999 and 2016, opioid-related mortality rate in Pennsylvania increased 50% per year.[66] This high rate is

widespread, with 78% of counties in the state having an overdose death rate higher than the national average in 2016.[67] However, there are county-wide differences in rates of overdose death. Six of the top ten counties with the highest rates are rural and the highest concentration of deaths are in the central and eastern parts of the state.[68] Trends in type of opioid used are similar to national trends. In 2018, most deaths were due to fentanyl and fentanyl analogs, followed by heroin and prescription opioids.[65] In regard to characteristics of those who died from a drug-related overdose, 29% were between the ages of 25 and 34 years, 70% were male and 79% were non-Hispanic white.[68] Although not specific to opioid use disorder, 82.5% of adults with a substance use disorder, other than alcohol use disorder, did not receive past year treatment (annual average, 2010-2014).[69]

To get a better understanding of potential influential factors contributing to the high rates of opioid overdose in the state, it is important to explore structural and social determinants of health in the state, including economic stability and opportunity, access to healthcare, as well as social and community contexts. In Pennsylvania, the median household income is $59,449 and 12.2% of the population is in poverty, both of these estimates are similar to the US as a whole. However, lower income and higher rates of poverty are heavily concentrated in the middle of the state where most counties are rural.[70] Twenty-one percent of the state is rural[71] and evidence from across the US suggests that rural areas have suffered from a heavy burden of opioid use disorder. This is impacted by many factors at the macro, local and micro levels. Of particular relevance, is the lack of access to health care, including medications to treat opioid use disorder.[72]

1.7 Overview of the Geisinger Health System and outpatient substance use treatment clinics

The Geisinger Health System (GHS) is a healthcare system that serves 38 counties in central, south-central and northeastern Pennsylvania. Within GHS, there are primary and specialty care clinics, free-standing community practice clinics, and over ten hospitals. The combined annual volume of emergency visits is over 250,000. GHS is also its own health insurance provider- Geisinger Health Plan, but provides care for all payer groups (e.g. Medicare, Medicaid, private health insurance). GHS provides health insurance to over 0.5 million members: approximately 50% of GHP's total membership is composed of Medicaid or Medicare members and approximately 40% of patients treated by the Geisinger Clinic also have Geisinger Health Plan coverage.[73]

To address the opioid crisis in the Geisinger Health coverage area, Geisinger opened four outpatient addiction treatment clinics between the years of 2017 and 2019 that offer medications, including buprenorphine and naltrexone to treat opioid use disorder. Since the opening of the first clinic in 2017, at least 2,700 patients with opioid use disorder have received treatment. The primary treatment model includes buprenorphine or naltrexone to treat OUD, as well as other medical interventions for detoxification and withdrawal, counseling services and care coordination.[74] Treatment protocols follow those of the American Society of Addiction Medicine. As of 2019, the average length of engagement across all patients (opioid use and alcohol use disorders) is approximately 220 days. Early data from the clinics show a reduction in all-cause mortality for patients treated for OUD, as well as improvements in other health domains (mental health, employment and social) according to the Addiction Severity Index.[74]

1.8 Prior studies assessing OUD and overdose using Geisinger Health System data

A few studies have used Geisinger Health System data to explore opioid use and related problems. Two studies assessed patterns of healthcare utilization[73] and risk factors[25] associated

with opioid overdose. Related to the study questions of this dissertation, one study that explored characteristics of persons who had experienced an overdose, found that 65% of patients had a mental illness prior to first overdose in their health records.[25] Interestingly, these researchers found that having a mental health disorder prior to first overdose was associated with a decrease in odds of death one year post-overdose.[25] In another study exploring patterns of healthcare utilization and costs of medical care before and after an overdose, Maeng and colleagues observed increases in emergency department visits, acute inpatient admissions and total medical costs occurred in the 1-2 years prior to opioid overdose that persisted following an overdose.[73] More specific to patients treated for chronic pain, two studies found that the lifetime prevalence of any prescription opioid use disorder was 41.3% and that major depression was associated with OUD.[75,76]

1.9 Summary and specific aims

As health systems like Geisinger work to expand treatment for OUD to reduce overall morbidity and mortality of these patients, more research is needed to understand their health needs, healthcare utilization and their course of opioid agonist treatment. This dissertation focuses on a vulnerable population of adults with co-occurring opioid use disorder and depression to understand how depression might play a role in healthcare utilization as well as continuity of buprenorphine treatment for OUD. All data came from the GHS, including electronic health records and prescription medication data ordered by health providers. All electronic health records for encounters and medication data within the GHS prior to the fall of 2019 were available.

Patients included in the study samples of each of the dissertation aims include adults recruited from one of GHS's four outpatient addiction treatment programs prior to the fall of

2019 to participate in a larger prospective study exploring clinical and genetic risk factors for opioid use disorder. The analyses conducted for this dissertation utilize this data to further our understanding of healthcare utilization and the course of buprenorphine treatment among individuals with co-occurring opioid use and depressive disorders. The dissertation specific aims are as follows:

Aim 1: The first study, Chapter 2 of this dissertation, describes person characteristics, health conditions and overall healthcare service utilization among patients with comorbid opioid use and depressive disorders, and assesses how these might differ among patients who have an opioid use disorder but no lifetime depressive disorder. This aim utilized all healthcare encounter data included in the electronic health records to describe patient characteristics, assess overall healthcare utilization and identify health conditions through diagnostic codes among adults with opioid use disorder and to compare differences between those with and without a co-occurring lifetime depressive disorder diagnosis. This study highlights important considerations when creating treatment plans and providing needed services for persons with co-occurring opioid use disorder and depression.

Aim 2: The second study, Chapter 3, explores differences in emergency department encounters and inpatient hospitalizations, overall and specific to mental health and substance use disorders, across time between adults with opioid use disorder with and without co-occurring depression. Using healthcare encounter data, this aim compares risk of different types of healthcare encounters in the time period following a person's first OUD diagnosis among

patients without a depression diagnosis prior to this OUD diagnosis and those with a depression diagnosis that preceded the OUD diagnosis. This study can help to inform potential unmet needs of persons with co-occurring opioid use disorder and depression based on differences in healthcare encounter utilization.

Aim 3: The third study, Chapter 4, examines differences in buprenorphine treatment continuity and retention among persons with OUD with and without co-occurring depression. This aim included data on prescription medications ordered by GHS providers to assess differences in risk of gaps in and discontinuation of buprenorphine treatment for OUD among patients who initiated treatment at one of Geisinger's outpatient addiction treatment centers, again comparing those with and without co-occurring depression. This study can inform treatment protocols to address both opioid use disorder and depression.

Chapter 2: Co-occurring depressive disorders among persons with opioid use disorder: Differences in characteristics, co-occurring health conditions and healthcare service utilization

2.0 Abstract

Background: Among persons with opioid use disorder, the most common co-occurring mental health disorder is depression. Co-occurring depression has been linked to greater risk of opioid misuse, overdose and suicide. However, less is known about characteristics, health conditions and healthcare utilization of persons with co-occurring opioid use disorder and depression.

Methods: This retrospective observational study included electronic health records (EHR) encounters from the Geisinger Health System in Pennsylvania that occurred prior to the fall of 2019 of patients recruited from one of Geisinger's outpatient addiction treatment clinics. All patients had at least one opioid use disorder (OUD) diagnosis in the EHR and were at least 18 years old at the date of first OUD diagnosis (N=721). Co-occurring depression was defined by having at least one depression diagnosis code in the EHR. Multivariable binary and ordinal logistic regression was performed to assess differences in person characteristics, other behavioral health and medical diagnoses, and healthcare utilization between individuals with and without comorbid depression.

Results: Forty-nine percent of the sample of persons with opioid use disorder had a lifetime depression diagnosis. Individuals with co-occurring depression were more likely to be female and have other medical conditions. Those with co-occurring depression were more likely to have other mental health and substance use disorders, as well as at least one overdose and/or suicide attempt or ideation. Persons with co-occurring disorders also had a greater number of outpatient and ED-related encounters compared to those with only OUD.

Conclusions: Opioid use and depressive disorders commonly co-occur. The current study identifies other comorbidities and health risks that are associated with co-occurring OUD and

depression, and highlights the need to consider these complex health needs when developing policies, services and treatment plans for persons with opioid use disorder.

2.1 Introduction

In 2018, 9.2 million adults in the United States had both a substance use and a mental health disorder.[11] Among adults with a substance use disorder almost half had a mental health disorder in the past year.[10] This is also true among persons with opioid use disorder (OUD). A recent study using the data from the National Survey on Drug Use and Health, 2015-2017, found that 64.3% of adults with OUD had any mental illness and 26.9% had a serious mental illness.[14] This study also found differences by demographic characteristics, including females and non-Hispanic white persons being more likely to have a co-occurring mental illness.

More specifically, substance use disorders and major depression commonly co-occur. A systematic review and meta-analysis using data from community settings, as well as inpatient and outpatient treatment settings from 1990 to 2019, found that among persons with major depressive disorder, alcohol use disorder was the most prevalent, followed by a substance use disorder involving drugs other than cannabis.[77] More limited information exists for the prevalence of depression among people with OUD. In studies using US national survey data, the lifetime prevalence of co-occurring OUD and major depressive disorder (MDD) has been shown to be as high as 50-60%.[15,16] In OUD treatment seeking or enrolled populations, current prevalence of MDD ranges between 20-30%.[17,18]

Psychiatric comorbidity among persons with substance use disorders is associated with reduced health-related quality of life, severity of mental health and substance use symptoms, and increased utilization of the emergency department.[19,78] This comorbidity is also associated with increased barriers to substance use and mental health treatment, and worse substance use treatment outcomes.[20–23] Specific to the relationship between opioid use disorder and depression,

co-occurring depression is associated with increased risk of opioid misuse, as well as non-fatal and fatal overdose and suicide.[21,24–28]

Despite extensive research examining co-occurring mental health and substance use disorders, most prior research on the burden and service use among individuals with such comorbidity has examined psychiatric comorbidity overall and fewer studies have explored specific co-occurring disorders, including opioid use disorder and depression. Because of this, we know less about the characteristics, additional health conditions and overall engagement with the healthcare system of persons with co-occurring opioid use disorder and depression, in particular, as compared to those who have opioid use disorder without a depressive disorder. As we continue to create policies and services to address the opioid crisis in the US, increasing our understanding of this comorbidity will play a critical role in enhancing services for individuals with both OUD and depression. To address this gap, the current study aimed to describe characteristics and overall healthcare service utilization among patients with co-occurring opioid use and depressive disorders, and assess how these might differ among patients who have an opioid use disorder but no lifetime depressive disorder.

2.2 Methods

Study design and sample selection

Data for this retrospective observational study were drawn from electronic health records (EHR) from the Geisinger Health System in Pennsylvania. The sample included EHR for all encounters that occurred within the Geisinger Health System prior to the fall of 2019 of patients who were recruited from one of Geisinger's medication-based treatment clinics to participate in a larger prospective study that aims to assess clinical and genetic risk factors for opioid use disorders. In addition to EHR, data on dispensed medications were used. Dispensed medication

history was extracted from Surescripts and includes a patient's dispensed medication history inside and outside of the Geisinger system. Medication information was available for most, but not all patients (n=697, 97%). Among these patients, the prior 24 months of dispensed medications from the requested date was provided.

The study sample was limited to patients who had an opioid use disorder diagnosis as defined by having at least one International Classification of Diseases ninth or tenth revision (ICD-9 or ICD-10) diagnostic code in their records and were at least 18 years old at the date of their first OUD diagnosis. The current study does not qualify as human subjects research as determined by Geisinger and Johns Hopkins Bloomberg School of Public Health Intuitional Review Boards.

Study measures

Independent variables

Opioid use and depressive disorder diagnoses. All patients in the study population had opioid use disorder. Patients were defined as having co-occurring opioid use and depressive disorder if they had at least one ICD-9 or -10 diagnosis code for a depressive disorder in the EHR. To ensure that our results did not change with a stricter case definition, we also conducted sensitivity analyses using a criterion of at least three ICD codes for depression over the study period to identify patients with depressive disorder.

A comprehensive list of all ICD-9 and -10 code used for each diagnosis is included in Supplemental Table 2.1. Inclusion of ICD codes was based on previous literature.[25,27,79–85]

Dependent variables

Opioid overdose included all accidental and non-accidental poisoning codes involving opioids, not including codes specific to adverse effects of an opioid. *Other mental disorder* diagnoses were defined by ICD codes related to all non-depressive mental disorders.

Other substance use includes all substance use disorder codes other than opioid use disorder. *Chronic pain* includes ICD codes for chronic pain. To define *other medical diagnoses*, codes were included for hypertension, diabetes mellitus, and disorders of the airway (chronic obstructive pulmonary disease (COPD) and asthma). Two *suicide-related diagnoses* were included, including attempts and ideations based on corresponding codes. To further understand the potential impact of a suicide attempt or ideation diagnostic code on diagnosis of depression, we explored the number of suicide attempt/ideation diagnostic codes that occurred before the date of the first depression diagnosis code, on the same date, or on a date following the first depression code. Of the 96 patients with at least one suicide attempt or ideation code, 49% had a depression code prior to the suicide diagnosis code. Thirty percent received these diagnoses on the same date, and 21% received a diagnosis for depression on a date following the suicide attempt/ideation diagnosis.

Dispensed medications. A patient was identified as having one or more dispensed buprenorphine prescriptions if at least one dispensed buprenorphine prescription was present in their record. A patient was identified as having one or more dispensed antidepressant prescriptions if at least one dispensed antidepressant medication was present.

Healthcare service utilization. The total length of care within the Geisinger Health System was calculated in years based on the first and last encounter dates within each record. We also calculated the total number of outpatient (OP), inpatient (IP) and emergency department (ED) encounters, as well as the number of OP, IP and ED encounters per year. Encounters that

were coded as ED to IP in the EHR were included in the ED-related visits for analyses because the initial contact was through the emergency department. For each encounter type, the total number was calculated, as well as the count within categories based on overall distribution across patients.

Demographic information. Patient demographic measures included within or derived from the EHR included sex, age at first OUD diagnosis, race, ethnicity, marital status and insurance coverage through the Geisinger Health Plan as of the date of consent for the larger study. Patients' age at first OUD diagnosis was categorized into the following age groups: 18-29, 30-39, 40-49, and 50 or older.

Analyses

First, length of time between first and last encounters, number of encounters per year, demographic characteristics, lifetime diagnoses for each condition, lifetime dispensed buprenorphine and antidepressant medications, as well as outpatient, inpatient and emergency department encounters were examined for the overall sample population, and separately for the OUD-only and co-occurring OUD and depression subgroups. Second, univariate associations between co-occurring OUD and depression and each dichotomous or categorical variable were examined using logistic regression models. To identify differences in characteristics, other comorbid conditions and health service use between the two groups, multivariable binary and ordinal logistic regression analyses, adjusting for age, sex, race, ethnicity, years between first and last EHR encounter and number of encounters per year were conducted. Multivariable models for healthcare service use additionally adjusted for other substance use diagnosis, other chronic pain diagnosis, other HIV/Hep C diagnosis, other medical comorbidity diagnoses. Confidence intervals were assessed at the 95% level and the measure of association was considered to be

statistically significant at a level of $p<0.05$. All analyses were conducted with Stata (version 14.2).

2.3 Results

Characteristics and health service utilization of the study sample

A total of 721 persons had at least one opioid use disorder diagnosis and were 18 years or older at the time of their first OUD diagnosis. Of these, 354 (49%) also had at least one depression diagnosis in their lifetime. Characteristics of the study sample are presented in Table 2.1, overall, as well as separately for patients who only had an OUD diagnosis and those with lifetime co-occurring OUD and depression. In the total sample, 52.4% were male and over 70% were under the age of 40. Ninety-nine percent of the sample was white and 85% of patients were not married. About 50% of all patients were enrolled in the Geisinger Health Plan. The mean number of years between the first and last Geisinger encounter across all patients was 11.7 years (Table 2.2). The mean number of all outpatient, inpatient and emergency department encounters was 51.7, with an average of 7.9 encounters per year.

Differences between OUD with and without co-occurring depression

There were a number of differences between persons diagnosed with OUD who had versus did not have co-occurring depression (Table 2.1). Those with co-occurring OUD and depression were more likely to be female (adjusted odds ratio (aOR)=0.53; 95% CI 0.38, 0.72), but did not differ on other demographic characteristics. Those with co-occurring OUD and depressive disorders had higher odds of having another medical comorbidity (aOR 2.00; 95% CI 1.42, 2.81). This was also the case for other mental (aOR 7.78; 95% CI 5.27, 11.54) and substance use (aOR 5.47; 95% CI 3.13, 9.55) disorders. There were also significant differences among groups in the prevalence of overdose, including those specific to opioids and other types

of overdose. Patients with co-occurring OUD and depression had higher odds of having at least one opioid overdose (aOR 3.38; 95% CI 1.79, 6.39), as was also the case with non-opioid overdose (aOR 2.75; 95% CI 1.51, 5.04). Similar results were also found for suicide attempt and ideation. Co-occurring disorders were associated with greater odds of having at least one suicide attempt and/or ideation code. Finally, while the majority of all patients had at least one dispensed buprenorphine prescription, those with co-occurring depression had decreased odds of at least one dispensed buprenorphine prescription (aOR 0.51, 95% CI 0.27, 0.94). Those with co-occurring depression were more likely to have received at least one dispensed antidepressant medication (aOR 5.90, 95% CI 3.89, 8.95) (Table 2.1).

The mean length of time in years between the first and last Geisinger encounter was greater for patients with co-occurring disorders (14.1 years vs. 9.5 years), as depicted in Table 2.2. Those with co-occurring disorders also had a greater number of outpatient and ED-related encounters compared to those with only OUD, after accounting of total length of time in the EHR as well as number of encounters per year.

2.4 Discussion

In this sample of patients with an opioid use disorder from a large integrated healthcare system in central Pennsylvania, almost half also had a lifetime diagnosis of depression. Further, after adjusting for length of time between first and last encounter in the EHR and number of encounters per year, we found significant differences between patients with only OUD and those with co-occurring OUD and depressive disorders with regard to other comorbidities, adverse health outcomes, and healthcare service utilization. Of particular concern, patients with lifetime co-occurring opioid use and depressive disorders had increased odds of having one or more opioid or non-opioid overdoses. These patients also had increased odds of having a code for

suicide attempt or suicide ideation within their electronic health records compared to patients who had an opioid use disorder but did not have a diagnosis for depression. This is consistent with previous research indicating that having a psychiatric comorbidity is associated with increased risk of non-fatal and fatal overdose,[26,27] as well as suicide.[28]

Other common medical conditions including hypertension, diabetes, COPD and asthma were also more prevalent among people with a co-occurring depressive disorder. These comorbidities have been shown in populations of people with both OUD and depression separately, but have been explored less frequently among those who have co-occurring disorders. Australian Treatment Outcome Study investigators found that overall physical and mental health was worse among heroin use disorder patients with comorbid depression than those without this comorbidity.[86] While not statistically significant in the adjusted models, chronic pain is another important comorbidity in this population. Chronic pain is common among persons with OUD and depression,[87–89] and among people with non-cancer chronic pain, depression has been shown to moderate the relationship between increased pain severity and opioid use.[90] The intersection between opioid use disorder, depression and chronic pain has significant implications for understanding the course and outcomes of all three conditions, as well as treatment plans to improve the health and well-being of individuals who are impacted. Integrated care models exist to address the complex healthcare needs of people who have co-occurring disorders, including integrating substance use and mental health care into primary care settings, integrating primary care into substance use and mental health services, as well as health homes which provide coordinated care for people with multiple health conditions, including substance use and mental health disorders.[91] The results of the current study underscore the importance of easily accessible integrated care for this population.

Persons with co-occurring opioid use and depressive disorders also utilized the emergency department in greater frequency, compared to those without a co-occurring depressive disorder. Opioid use and depressive disorders are associated with more frequent emergency department use, and present unique health risks including overdose.[27,92,93] This might be related to severity of opioid use or depressive disorder and other added comorbidities experienced by these individuals. Additionally, adverse outcomes of depression and opioid use disorder, including suicide ideations and attempts, and non-fatal overdose could influence service use.[94–96] Greater use of emergency services in this comorbid group may also be related to the larger number and types of barriers to accessing needed healthcare that individuals face, including cost of care, inconvenience of service location or hours, as well as negative views from others.[23] Whatever the reasons for the increased use of services in the group of patients with co-occurring opioid use and depressive disorders, our results suggest that this population experiences a greater burden of OUD and would likely benefit from highly-integrated services that meet their multiple needs. Integrated care creates the opportunity for greater provider coordination and could prevent frequent use of emergency and inpatient services, and improve patients' quality of life—opportunities that may be far less available in other health care settings where substance use treatment, mental health services, and other medical care are typically separate and far less integrated than in the Geisinger Healthcare System.

Limitations

There are many advantages of using EHR, including the ability to follow patients longitudinally and the capacity to assess real-world utilization patterns. However, there are also a number of limitations that need to be acknowledged. For information on diagnoses, this study relies on ICD codes and provider documentation of these codes, which could be influenced by

provider diagnostic and practice styles, as well as requirements of health insurance billing. Related to this point, EHR data is not collected for research purposes and thus EHR diagnoses using ICD codes may differ from those collected in a more traditional diagnostic interview. However, because this population was recruited from an outpatient substance use treatment clinic, addiction specialists verified the OUD diagnosis. Additionally, we were only able to assess characteristics and diagnostic codes included in the EHR; there are many other health system- and person-level factors that that we were not able to assess. It is possible that individuals received care at one point or another from a non-Geisinger healthcare system, or could have died during the study period, which would not be captured in the EHR used for this study. Additionally, the time observed within the EHR for each person is not consistent. However, we did adjust for length between first and last visit and number of encounters per year. The sample of the current study includes almost exclusively white patients from rural Pennsylvania. Because of this, the results may not generalize to more racially diverse and urban populations. Finally, this sample is limited to persons who were seeking care at a medication-based treatment program for opioid use disorder. Therefore, the results might also not generalize to persons who do not have access to these clinics and may face greater barriers accessing care.

Conclusions

Opioid use and depressive disorders commonly co-occur. As we continue to develop policies and services to reduce the morbidity and mortality associated with the opioid epidemic, we should also be considering ways to address comorbid mental health disorders, and depression in particular. This study highlights the characteristics and health service use patterns of individuals with co-occurring opioid use and depression that are essential to consider when creating treatment plans and providing needed services.

Table 2.1 Sample characteristics and differences between patients with opioid use disorder with and without lifetime depression

	Overall (N=721)	**OUD only (n=367)[a]**	**OUD+DEP (n=354)[b]**		
	%	*%*	*%*	*Unadjusted OR (95% CI)[c]*	*Adjusted OR (95% CI)[c,d]*
Sex					
Female	47.6	39.2	56.2		
Male	52.4	60.8	43.8	**0.50 (0.37, 0.67)*** **	**0.53 (0.38, 0.72)*** **
Age[e]					
18-29	36.6	36.2	37.0	1.00	1.00
30-39	36.8	40.0	34.5	0.87 (0.62, 1.22)	0.82 (0.56, 1.18)
40-49	15.4	14.7	16.1	1.07 (0.69, 1.67)	1.00 (0.62, 1.62)
50 or older	11.2	10.1	12.4	1.21 (0.73, 1.99)	1.28 (0.75, 2.21)
Race					
Other	0.97	1.1	0.9		
White	99.0	98.9	99.1	1.29 (0.29, 5.80)	0.33 (0.03, 3.42)
Ethnicity					
Hispanic or Latino	2.5	3.3	1.7		
Not Hispanic or Latino	97.5	96.7	98.3	1.96 (0.73, 5.28)	0.97 (0.31, 3.08)
Marital status					
Not Married	85.4	85.9	85.9		
Married	14.6	15.1	14.1	0.93 (0.61, 1.40)	0.87 (0.55, 1.37)
Geisinger insurance					
No	46.9	49.3	44.5		
Yes	53.1	50.7	55.5	1.21 (0.91, 1.63)	1.13 (0.82, 1.55)
Opioid Overdose[f]					
Zero	91.5	95.4	87.6		
One or more	8.5	4.6	12.4	**2.92 (1.64, 5.22)*** **	**3.38 (1.79, 6.39)*** **
Non-Opioid Overdose[g]					
Zero	90.6	95.4	85.6		
One or more	9.4	4.6	14.4	**3.46 (1.96, 6.13)*** **	**2.75 (1.51, 5.04)*** **
Other MH disorder dx[h]					
Zero	37.2	60.5	13.0		
One or more	62.8	39.5	87.0	**10.25 (7.05, 14.90)*** **	**7.78 (5.27, 11.54)*** **
Other SU disorder dx					
Zero	17.6	29.7	5.1		
One or more	82.4	70.3	94.9	**7.89 (4.67, 13.32)*** **	**5.47 (3.13, 9.55)*** **

Suicide attempt dx					
Zero	94.6	98.4	90.7		
One or more	5.4	1.6	9.3	**6.19 (2.56, 14.95)*** **	**5.01 (2.01, 12.53)*** **
Suicide ideation dx					
Zero	89.6	99.2	79.7		
One or more	10.4	0.8	20.3	**30.98 (9.66, 99.35)*** **	**35.62 (10.85, 116.89)*** **
Suicide attempt or ideation dx					
Zero	86.7	97.6	75.4		
One or more	13.3	2.4	24.6	**12.96 (6.41, 26.21)*** **	**13.92 (6.71, 28.88)*** **
Chronic pain dx					
Zero	69.6	76.3	62.7		
One or more	30.4	23.7	37.3	**1.91 (1.38, 2.64)*** **	1.37 (0.95, 1.98)
HIV or Hep C dx					
Zero	81.1	84.7	77.4		
One or more	18.9	15.3	22.6	**1.62 (1.11, 2.37)***	1.34 (0.89, 2.01)
Other med dx[i]					
Zero	58.5	70.0	46.6		
One or more	41.5	30.0	53.4	**2.68 (1.97, 3.63)*** **	**2.00 (1.42, 2.81)*** **
Dispensed bup rx					
Zero	8.2	6.3	10.0		
One or more	91.8	93.7	90.0	0.61 (0.35, 1.05)	**0.51 (0.27, 0.94)***
Dispensed anti-dep rx					
Zero	28.4	45.4	11.5		
One or more	71.6	54.6	88.5	**6.42 (4.34, 9.50)*** **	**5.90 (3.89, 8.95)*** **

***p<0.001, **p<0.01, *p<0.05

[a] Opioid use disorder (OUD)

[b] Opioid use disorder and Depression (OUD+DEP)

[c] Odds of each characteristic, diagnosis, and dispensed medication in the OUD with depression group relative to the odds of each in the OUD without depression group; OR refers to odds ratio and aOR refers to adjusted odds ratio

[d] Adjusted models include age, sex, race, ethnicity, number of encounters per year, and total length of care between first and last GHS encounter dates

[e] Age at first opioid use disorder diagnosis

[f] Includes any opioid poisoning ICD9 or ICD10 code

[g] Includes any poisoning ICD9 or ICD10 code, not specific to opioids

[h] Excludes depressive disorders, but includes other mood disorders (402, 55.3% have at least one mood disorder dx)

[i] Includes hypertensive disease, diabetes mellitus, and other disorders of the airway (i.e. COPD and asthma) ICD9 or ICD10 codes

Table 2.2 Healthcare service utilization comparing patients with opioid use disorder with and without lifetime depression

	Overall (N=721)	**OUD only (n=367)**	**OUD+DEP (n=354)**		
	Mean (sd)	*Mean (sd)*	*Mean (sd)*	*Unadjusted OR/IRR (95% CI)[b]*	*Adjusted OR/IRR (95% CI)[b,c]*
Number of GHS encounters[a]	51.7 (47.5)	32.7 (27.6)	71.5 (55.2)	**2.19 (1.95, 2.47)*** **	0.97 (0.83, 1.13)
Number of encounters per year	7.9 (17.9)	10.1 (24.5)	5.7 (4.6)	**0.57 (0.44, 0.73)*** **	0.87 (0.73,1.03)
	%	*%*	*%*		
Outpatient encounters					
0-9	13.7	21.8	5.4	**4.36 (3.30, 5.78)*** **	**2.06 (1.51, 2.82)*** **
10-19	20.7	25.9	15.3		
20-29	15.3	19.9	10.5		
30-39	12.6	11.7	13.6		
40 or more	37.7	20.7	55.4		
Inpatient encounters					
0	42.4	54.2	30.2	**2.80 (2.12, 3.70)*** **	1.22 (0.89, 1.68)
1-2	29.0	27.5	30.5		
3 or more	28.6	18.3	39.3		
Emergency department encounters					
0	19.7	27.8	11.3	**2.97 (2.26, 3.92)*** **	**1.51 (1.11, 2.06)** **
1-5	38.8	43.6	33.9		
6-9	15.7	12.3	19.2		
10 or more	25.8	16.4	35.6		

***p<0.001, **p<0.01, *p,0.05

[a] Includes outpatient, inpatient and emergency department encounters

[b] Models examined the odds of each healthcare service outcome in OUD with depression group relative to the odds of each healthcare service outcome in OUD without depression group

[c] Adjusted models include age, sex, race, ethnicity, any other SU dx, any chronic pain dx, any HIV/Hep C dx, any other Medical dx, length of time in years between first and last encounter

Supplemental Table 2.1 ICD 9 and ICD 10 codes used to define diagnoses

Diagnosis categories	Diagnosis Included
Mental health and Substance use	
Opioid use disorder	ICD9: 304, 304.0, 304.00-.02, 305.5, 305.50-.52 ICD10: F11, F11.1, F11.10, F11.12, F11.120-.122, F11.129, F11.14, F11.15, F11.150-.151, F11.159, F11.18, F11.181-.182, F11.188, F11.19, F11.2, F11.20, F11.22, F11.220-.222", F11.229, F11.23-.25, F11.250-.251, F11.259, F11.28, F11.281-.282, F11.288, F11.29, F11.9, F11.90, F11.92, F11.920-.922, F11.929, F11.93-.95, F11.950-.951, F11.959, F11.98, F11.981-.982, F11.988, F11.99
Depressive disorders	ICD9: 296.2*, 296.3*, 300.4*, 311 ICD10: F32*, F33*, F34.1
Other substance use disorder	ICD9: 303*, 304.1*, 304.2*, 304.3*, 304.4*, 304.5*, 304.6*, 304.8*, 304.9*, 305.0*, 305.1*,305.2*, 305.3*, 305.4*, 305.6*, 305.7*, 305.9* ICD10: F10*, F12*-F19*, F55*
Other mental health disorder	ICD9: 290*-296*, 297*-299*, 300*, 301*, 302*, 308*, 309* ICD10: F01*-F09*, F20*-F25*, F28*-F29*, F31*, F34*, F39, F40*, F41.0, F41.1, F41.3, F41.8, F41.9, F42*-F45*, F48*, F50*-F52*, F54*, F59*, F60*, F63*-F69*, F99*
Suicide attempt	ICD9: E950*-E958* ICD10: T14.91*, X71*-X83*
Suicide ideation	ICD9: V62.84 ICD10: R45.851
Overdose	
Opioid overdose	ICD9: 965, 965.0, 965.01, 965.09, E850.0, E850.2 ICD10: T40.0X1*, T40.0X2*, T40.0X4*, T40.1-.4*, T40.6*
Other drug overdose	ICD9: 965.1, 965.4, 965.5, 965.6*, 965.7-.9, 967*, 968*, 969*, 969.4, 970*, 970.81 980*, 981, 982*, E850.3-.9, E851, E852*, E853*, E854*, E855.1, E858.8-.9, E860*, E862*, E980*, E980.0-.5 ICD10: T39.011*, T39.012*, T39.014*, T39.091*, T39.092*, T39.094*, T39.4X1*, T39.4X2*, T39.4X4*, T39.8X1*, T39.8X2*, T39.8X4*, T39.91*, T39.92*, T39.94*, T40.5X1*, T40.5X2*, T40.5X4*, T40.7X1*, T40.7X2*, T40.7X4*, T40.8X1*, T40.8X2*, T40.8X4*, T40.901*, T40.902*, T40.904*, T40.991*, T40.992*, T40.994*, T41.0X1*, T41.0X2*, T41.0X4*, T41.1X1*, T41.1X2*, T41.1X4*, T41.201*, T41.202*, T41.204*, T41.291*, T41.292*, T41.294*, T41.3X1*, T41.3X2*, T41.3X4*, T41.41*, T41.42*, T41.44*, T42.3X1*, T42.3X2*, T42.3X4*, T42.4X1*, T42.4X2*, T42.4X4*, T43.601*, T43.602*, T43.604*, T43.621*, T43.622*, T43.624*, T43.631*, T43.632*, T43.634*, T43.641*, T43.642*, T43.644*, T43.691*, T43.692*, T43.694*, T43.8X1*, T43.8X2*, T43.8X4*, T43.91*, T43.92*, T43.94*
Other medical	
Chronic pain	ICD9: 338.2*, 338.4, ICD10: G89.2*, G89.4
HIV and Hepatitis C	ICD9: 042, 070.41, 070.44, 070.51, 070.54, 070.71 ICD10: B20, B17.1*, B18.2, B19.2*
Other *(includes hypertensive disease, diabetes mellitus, disorders of the airway-COPD and asthma)*	ICD9: 401*-405*, 205*, 490*-496* ICD10: I10*-I13*, I15*-I16*, E08*-E11*, E13*, J40*-J45*, J47*

Supplemental Table 2.2 Predicted probabilities of number of outpatient, inpatient and emergency department visits comparing OUD without depression and OUD with depression

	OUD only (n=367)	**OUD+DEP (n=354)**
	Predicted Probability [95% CI]	Predicted Probability [95% CI]
Outpatient encounters		
0-9	0.09 (0.01) [0.07,0.12]	0.05 (0.01) [0.03, 0.06]
10-19	0.25 (0.02) [0.21, 0.29]	0.15 (0.02) [0.12, 0.19]
20-29	0.23 (0.02) [0.19, 0.27]	0.19 (0.02) [0.16, 0.23]
30-39	0.18 (0.02) [0.14, 0.21]	0.20 (0.02) [0.16, 0.24]
40 or more	0.25 (0.02) [0.21, 0.30]	0.41 (0.03) [0.35, 0.47]
Inpatient encounters		
0	0.43 (0.03) [0.37,0.49]	0.38 (0.03) [0.33, 0.44]
1-2	0.36 (0.02) [0.32, 0.41]	0.38 (0.02) [0.33, 0.42]
3 or more	0.20 (0.02) [0.16, 0.25]	0.24 (0.02) [0.19, 0.29]
ED encounters		
0	0.15 (0.02) {0.12, 0.19]	0.11 (0.01) [0.08,0.13]
1-5	0.52 (0.02) [0.48, 0.57]	0.47 (0.03) [0.42, 0.52]
6-9	0.16 (0.02) [0.15, 0.22]	0.20 (0.02) [0.16, 0.23]
10 or more	0.16 (0.02) [0.13, 0.20]	0.22 (0.02) [0.18, 0.27]

Chapter 3: Emergency department and inpatient service utilization among persons with co-occurring opioid use and depressive disorders

3.0 Abstract

Background: In recent years, emergency department visits involving opioid overdose have increased. Co-occurring mental illness is associated with increased risk of overdose, as well greater emergency department utilization among persons with substance use disorders. Because depression is a common co-occurring mental illness among persons with opioid use disorder, this study aimed to assess the role of depression in the utilization of emergency department and inpatient services among persons with opioid use disorder.

Methods: Electronic health records from the Geisinger Health System in Pennsylvania were obtained for patients who had at least one opioid use disorder diagnosis in their records (N=613). Co-occurring depression was defined by having a depression diagnosis prior to first opioid use disorder diagnosis. Propensity score weighted Cox regression survival analysis for recurrent events was used to assess differences in risk for healthcare service utilization comparing those with and without prior depression.

Results: Compared to opioid use disorder without prior depression, opioid use disorder with prior depression was associated with increased risk of emergency department visits that included a substance use diagnosis, suicide ideation or attempt code, and/or other mental health disorder codes.

Conclusions: Co-occurring depression is associated with greater risk of emergency department utilization related to effects of substance use and mental health disorders. This increased risk could be influenced by the unmet need for treatment, as well as complex treatment needs of persons with co-occurring opioid use disorder and depression. Further exploration is needed to

understand the role of depression in the use of these healthcare services and how integration of depression care into medical care and treatment for opioid use disorder can mitigate this risk.

3.1 Introduction

Despite the small decrease in drug overdose deaths from 2017 to 2018 in the US, over 65,000 people in the US died from an overdose in 2018 and 70% of these deaths involved an opioid.[97] In the recent years of the US opioid crisis, the prevalence of opioid-related emergency department visits and inpatient hospitalizations have continued to increase. Between 2005 and 2014, the rate of opioid-related inpatient hospitalizations increased 64.1% and opioid-related ED visits increased 99.4%.[5] More recently from July 2016 to September 2017, emergency department visits that involved an opioid overdose increased by 30% in the US overall.[98] Emergency department utilization is of high importance because of potential implications related to greater symptom severity, inadequate management of health conditions, increased risk of hospitalization, as well as greater use of the health system overall.[29] In regard to the opioid crisis, understanding emergency department use and inpatient hospitalizations among persons who use opioids is of particular value, as it can inform jurisdictions of potential changes in opioid-related consequences, including non-fatal and fatal overdose, and serve as an early intervention point for individuals who are most at risk.[98,96,99]

Co-occurring mental illness is a contributing factor to increased emergency department utilization among people with substance use disorders.[29,30] Mental illness among persons with opioid use disorder (OUD) is common,[14] and in addition to impacts on healthcare service utilization, this comorbidity can lead to heighted risk of morbidity and mortality.[19,25] Depression is the most common mental health disorder that co-occurs with OUD,[18] and associated with risk of overdose and suicide in this population.[25,26,28] There is also unmet need for treatment of depression among persons with substance use disorders, including OUD, with 55% of people with co-occurring major depressive episodes and substance use disorder reporting past year

treatment for depression.[31] This unmet treatment need could be impacting the utilization of emergency department and inpatient services, as well as contribute to risk of adverse outcomes.

Because of the increased prevalence of a co-occurring depressive disorder among adults with opioid use disorder, as well as the complex health needs, it is important to further explore how this population utilizes emergency department and inpatient healthcare services. Extensive literature exists that explores ED use among persons with substance use and mental illness broadly, but despite this, we know less about the specific role depression plays in the use of emergency department and inpatient services among persons with OUD. Further, limited information is available about specific reasons for the use of ED and inpatient services among those with co-occurring disorders, and more specifically those with OUD and depression. To address these gaps in our knowledge, this retrospective cohort study sought to understand the role of depression in healthcare service utilization among persons with opioid use disorder. This study aimed to explore differences in types of healthcare encounters, including emergency department and inpatient encounters overall and those specific to mental health and substance use disorders over a period of a number of years utilizing electronic health records from a large integrated healthcare system in Pennsylvania.

3.2 Methods

Study design and setting

Data were drawn from the Geisinger Health System in Pennsylvania. The study sample included patients who were recruited from one of Geisinger's four medication-based substance use treatment programs prior to the fall of 2019 to participate in a larger prospective study exploring clinical and genetic risk factors for opioid use disorder. All electronic health records for encounters within the Geisinger Health System prior to the fall of 2019 were available.

Electronic health records (EHR) were limited to adults with an opioid use disorder (OUD) diagnosis in their records, who were at least 18 years old on the day of their first OUD diagnosis and had at least 12 months of EHR data prior to their first OUD diagnosis code in the health records (N=613). An OUD diagnosis was determined according to International Classification of Diseases Ninth and Tenth Revisions Clinical Modification (ICD-9-CM and ICD-10-CM). A list of all diagnostic codes for OUD used in the study is included in Supplemental Table 3.1. All healthcare encounters, including outpatient, inpatient and emergency department visits within the Geisinger Health System, records that occurred prior to a person's first OUD diagnosis date were used to define exposure groups. Encounter records that occurred on or after a person's first OUD diagnosis date were included in time to event analyses. The final analytic dataset resulted in a total of 608 individual patients, who had encounters following their OUD diagnosis, with 21,058 total encounters over an average of 872 days between first OUD diagnosis and last EHR encounter. Across all patients, the dates of first OUD diagnosis ranged from July 16, 1998 to August 9, 2019. Dates of last EHR encounter ranged from May 12, 2018 to September 20, 2019. The current study did not qualify as human subjects research as determined by Geisinger and Johns Hopkins Bloomberg School of Public Health Intuitional Review Boards.

Independent and outcome measures

The primary exposure variable of interest was a depression diagnosis code prior to the date of first OUD diagnosis. This was defined in two ways: 1) Any depression diagnosis code prior to first OUD diagnosis; 2) Any depression diagnosis code within 12 months prior to first OUD diagnosis. Other covariates included the following: sex, age at OUD diagnosis date, race, ethnicity, mental illness (MI) (other than depression), substance use disorder (SUD) (other than opioid use disorder), HIV or Hepatitis C diagnosis, chronic pain diagnosis, and other common

medical diagnoses (hypertension, diabetes mellitus, and disorders of the airway (chronic obstructive pulmonary disease (COPD) and asthma), all prior to date of first OUD diagnosis. All medical and mental health and substance use diagnoses were defined using ICD 9 or 10 codes listed in Supplemental Table 3.1. Prior buprenorphine medication to treat opioid use disorder was also included by incorporating data from ordered prescriptions from Geisinger and dispensed prescriptions that could have been ordered inside or outside of the Geisinger Health System. For the purposes of our study, we categorized persons as having a buprenorphine prescription if they had at least one ordered or dispensed buprenorphine medication prior to first OUD diagnosis.

We assessed the following outcomes that occurred after a person's first OUD diagnosis date: 1) All emergency department (ED) encounters; 2) Overdose-related ED encounters defined as having an opioid or non-opioid poisoning code at an ED encounter; 3) Suicide-related ED encounters defined as having a suicide attempt or ideation code at an ED encounter; 4) Mental illness-related ED encounter defined as having a mental health disorder code (including depression) at an ED encounter; 5) Substance use-related ED encounter defined as having a substance use disorder code (excluding OUD) at an ED encounter; 6) All inpatient (IP) encounters; 7) Mental illness-related IP encounters; 8) Substance use-related IP encounters; 9) All suicide (attempt or ideation) related encounters; 10) All overdose (opioid or non-opioid poisoning) encounters.

Data Analyses

Propensity score weighting. First, to account for potential confounding variables and to create exposure groups with balanced distribution of observed covariates, stabilized inverse probability of treatment weights (IPTW) for OUD with prior depression were calculated from

propensity scores derived using logistic regression. For all prior depression, propensity scores were constructed using patient characteristic variables at the date of origin (first date of OUD diagnosis) and relevant diagnoses, including other mental health disorders, other substance use disorders, medical conditions, HIV or Hepatitis C, and chronic pain, as well as any received buprenorphine prescriptions that occurred prior to the origin. For past year depression, only diagnosis codes that occurred with the year prior to first OUD diagnosis were included. After applying IPTW, we observed substantial reductions in differences in the distribution of covariates between the OUD without and OUD with prior depression groups. Crude and standardized differences in covariate proportions are presented in Supplemental Tables 3.2 and 3.3. Absolute standardize differences are often used to examine covariate balance after applying propensity score methods. Two thresholds, 0.1 and 0.25 have been identified in prior research for identifying imbalance.[100] After applying weights for all prior depression all standardized differences were less than 0.1. After applying weights for past year depression, the standardized difference for sex was greater than 0.25 and the absolute standard differences for age category 40-49, past year mental health and substance use disorders, and past year buprenorphine were greater than 0.1 (Supplemental Table 3.3). To account for potential imbalance after applying weights, we also included these variables in the regression models for past year depression.

Time to event models. We conducted a propensity score weighted Cox regression survival analysis for recurrent events. Risk set entry was the date of first OUD diagnosis and the exit date was the date of last encounter in the EHR. To assess the association between OUD with prior or past year depression and each outcome, we utilized an extension of the Cox proportional hazards model: the Prentice, Williams and Peterson (PWP) model to estimate the crude and stabilized inverse probability of treatment weighted hazard ratios. Because of the recurrent nature of the

events of interest, the utilization of the original Cox proportional hazards model is limited due to the independence assumption. Because of this assumption the original model is only appropriate for modeling time to the first event. The PWP model analyzes ordered multiple events by stratifying based on the number of prior events in the follow-up period.[101] For our study question, the total time model was fitted to assess the effect of all prior/past year depression for each ordered event since entry into the risk set (OUD diagnosis). Robust standard errors were also applied to account for clustering because of multiple encounters per patient.[102] Cumulative hazard plots were used to visually display the cumulative hazard function for each event over time for each exposure group.

Sensitivity analyses. A number of sensitivity analyses were completed to assess the sensitivity of results to lack of information about possible history of OUD and other factors before the original diagnosis in the Geisinger system and the inability to confirm temporal pattern of diagnoses. For these sensitivity analyses we created two additional sets of IPTWs that excluded 1) mental health diagnoses, other than depression and 2) mental health and substance use disorders, other than depression and OUD. Therefore, these sets of IPTWs were limited to covariates likely not impacted by depression. We also ran a number of models to assess differences in hazard ratios for each outcome. First to account for small risk sets toward the end of the observation period, we truncated follow-up time to 10 years after first OUD diagnosis. Second, because persons with the OUD without prior/past year depression group could develop and receive a depression diagnosis following their first OUD diagnosis, we conducted models excluding depression episodes following first OUD diagnosis in the OUD without prior depression exposure group, therefore setting the exit date to date of first depression diagnosis or date of last GHS encounter. By excluding these depression episodes, the OUD without

depression group was limited people who did not have any (prior or following) depression codes in their EHR.

3.3 Results

Sample characteristics

Sample characteristics of persons with any prior depression (43.6%), past year depression (17.0%) and no depression prior to first opioid use disorder diagnosis (56.4%) are presented in Table 3.1. There were a number of differences between groups. Patients with OUD and prior depression were more likely to female. Patients with OUD and prior depression were also more likely to have the following prior diagnoses: mental health and substance use disorders, medical diagnoses (diabetes, hypertension, COPD and/or asthma), and chronic pain (Table 3.1).

Risk of health service utilization outcome by OUD+ Prior DEP

Across all patients, there were a total of 1,225 emergency department encounters and 515 inpatient encounters that occurred during the follow-up period. 73.2% of emergency department encounters (n=897) and 28.5% of inpatient encounters (n=147) included a mental illness or substance use disorder code. Suicide-related encounters, including encounters for suicidal ideation and attempt, and overdose, were less prevalent. Across time, 56 encounters included a suicide attempt or ideation code and 56 encounters included an overdose code. The frequency of healthcare encounters at the patient level are presented in Table 3.2.

Table 3.3 presents incidence rates, and crude and weighted hazard ratios for each healthcare encounter. The weighted hazard of suicide ED encounters was significantly higher among persons with any prior or past year depression compared to those without prior depression (any prior depression hazard ratio [HR]=2.80, 95% confidence interval [CI]=1.35-5.80; past year depression HR=11.93, CI=1.56, 91.04). This was also the case with substance use-related ED

encounters (any prior depression HR=1.59, CI=1.04-2.44; past year depression HR=1.76, CI=1.11, 2.08). The weighted hazard of an ED encounter including a mental health or substance use disorder code was significantly higher among those with past year depression compared to those without prior depression (HR=1.70, CI=1.07-2.69). To display these selected results graphically, the weighted cumulative hazard plots are displayed in Supplemental Figure 3.1.

Sensitivity analyses results

The analyses with IPTW that excluded prior/past year mental health or substance use disorder diagnoses changed slightly. All HRs were in the same direction but statistical significance was not met for all. Weighted results did not change significantly when follow-up time was truncated to 10 years post first OUD diagnosis. However, after excluding depression episodes post OUD diagnosis among patients without a prior depression diagnosis, the weighted HRs for MI inpatient encounters and any overdose encounter became statistically significant, and the weighted HR for MI ED encounters was no longer statistically significant. For past year depression, results were similar. The changes for any prior depression may suggest that we are underestimating the effect of depression because we included persons with the OUD with prior depression group who received a depression diagnosis following their first OUD diagnosis.

3.4 Discussion

The present study examined the association between opioid use disorder with a prior depression diagnosis and risk of utilization of the emergency department and inpatient healthcare services for mental health and substance use disorders, as well as overdose- and suicide- related reasons within the Geisinger Health System in Pennsylvania. We found that a prior depression diagnosis was associated with increased risk of emergency department visits that included a substance use diagnosis or suicide ideation or attempt code, and/or other mental health and

substance use disorder codes. Our results align with previous research suggesting that persons with co-occurring substance use and mental health disorders utilize emergency services at greater frequency[30,99] and that psychiatric comorbidity may influence increased risk of overdose.[24–27] This study uniquely contributes to our understanding of the association between depression diagnosis and particular types of emergency department visits. The results suggest that assessing and treating depression could be an important factor in reducing later risk of overdose, as well as emergency department use among people with opioid use disorder.

We found that persons with OUD and any prior or past year depression had a higher rate of emergency department visits that included a substance use code not related to opioids. Of this sample of adults, 89% of those with both OUD and any prior depression and 92% of those with a past year depression code had a prior substance use disorder code that was not opioid use disorder in their health records. This is similar to results from nationally represented data. A study utilizing the National Survey on Drug Use and Health (NSDUH) from 2002 to 2013 found that among persons who used heroin, 96% reported using at least one other substance and 61% reported using three or more other substances in the past year. Thirty-five percent also met criteria for alcohol use disorder and 25% for cocaine use disorder in the past year.[103] Additionally, fatal overdoses involving stimulants and benzodiazepines have increased in recent years,[64] with the majority of these overdoses also involving an opioid.[104] While we know that the use of other substances is not uncommon among persons who use opioids, the role of depression in this association is less well understood. Future research should continue to assess the specific contribution of depression to the prevalence and severity of other co-occurring substance use disorders and to the heightened risk of overdose in these individuals.

Prior depression among patients with OUD was also associated with increased hazard of emergency department visits with a suicide attempt or ideation code, and while not statistically significant was positively associated with encounters that involved an overdose, whether involving opioids or not. While not surprising given the existing research that has found an association between depression, and suicide and overdose,[24,28] this finding suggests that co-occurring depression is associated with these adverse outcomes among the vulnerable group of individuals with OUD. The potential link between suicide and overdose is an important one to consider. Although classification challenges exist,[62,105] national trends depict an increase in rates of both suicide and unintentional overdose over the past two decades[64,106] and it is estimated that between 21-33% of overdose deaths may be intentional.[28,62,63] Persons with OUD have increased risk of suicide, particularly after experiencing a non-fatal overdose.[107] Further, the use of prescription opioids could be motivated by unmet treatment need for depression, as demonstrated by a qualitative study that interviewed relatives or friends of persons who died from an overdose involving prescription opioids.[63] In the US, 55% of adults with a substance use disorder and co-occurring major depressive episodes receive treatment for depression,[31] and specific to the use of antidepressants to treat depression, challenges with treatment continuation exist with less than 30% of adults continuing antidepressant treatment for longer than three months.[108] While having an antidepressant prescription at least once during the study period was relatively common in our study sample, this does not necessarily indicate continuous treatment and also does not capture potential participation in other forms of treatment for depression. Future research is needed to understand the impact of treatment for depression, including continuity of antidepressant use, on suicide and overdose outcomes among this population of adults with co-occurring opioid use disorder and depression. These results also suggests the importance of ensuring suicide

prevention is integrated into treatment protocols. Overall emphasis on managing mental health disorders, particularly depression, in this population and acknowledging the role of depression in developing prevention initiatives for opioid overdose and suicide is critical.

Limitations

Along with notable strengths of using EHR data to assess our study question, including the ability to examine healthcare utilization over time, there are a number of limitations that need to be recognized. First, EHR diagnoses are based on health care providers' recorded ICD codes. Clinicians vary widely with regard to the accuracy of their recorded diagnoses. Second, while throughout the text we refer to the first date of opioid use disorder, this denotes to the first opioid use disorder code within the Geisinger Health System. We cannot conclude that this was a person's first ever diagnosis and we also cannot assume that a person did not have OUD prior to this date, as they could have had an undiagnosed disorder or a diagnosis not included in the Geisinger EHR. Additionally, differences in observation time prior to first OUD diagnosis could impact likelihood of receiving diagnoses because of differences in contact with the health system. While some of this variation could be accounted for by including age in the propensity score model, as well as limiting to past year diagnoses; we will account for this in future planned analyses. Also, because of how our exposure groups were defined, patients in the OUD without prior depression group could have received a depression diagnosis at a later date. Our choice of using prior depression as the exposure was done to avoid the possibility of OUD leading to the first diagnosis of depression. Our sample size and number of events were also relatively small and follow-up time was relatively short, which could have limited statistical power and therefore influence the ability to reach statistical significance for some of the healthcare service outcomes. Lastly, the study sample includes almost exclusively white non-Hispanic patients receiving

healthcare in rural Pennsylvania, which may limit generalizability to more racially diverse and urban populations.

Conclusions

Because of the high comorbidity between opioid use disorder and depression,[16] and recent increases in opioid related-emergency department and inpatient hospitalizations,[5] it is important to understand the potential role of depression in the use of these healthcare services, as well as the adverse outcomes associated with this comorbidity including suicide and overdose. The influence of depression comorbidity is complex and warrants further exploration. Despite this complexity, it is clear that management of depression and incorporating mental health services into medical care and OUD treatment, as well as overdose prevention efforts is needed.

Table 3.1 Sample characteristics by depression exposure group (N=613)

	OUD wo prior DEP (n=346) n (%)	OUD w prior DEP (n=267) n (%)	OUD w past year DEP (n=104) n (%)	Unadjusted Odds Ratio (95% CI)[a]	Unadjusted Odds Ratio (95% CI)[b]
Sex					
Female	140 (40.5)	161 (60.3)	59 (56.7)	1.00	1.00
Male	206 (59.5)	106 (39.7)	45 (43.3)	**0.45 (0.32, 0.62)**	**0.52 (0.33, 0.81)**
Age group[c]					
18-29	131 (37.9)	92 (34.5)	35 (33.7)	1.00	1.00
30-39	125 (36.1)	98 (36.7)	41 (39.4)	1.12 (0.77, 1.63)	1.23 (0.73, 2.05)
40-49	55 (15.9)	40 (15.0)	15 (14.4)	1.04 (0.64, 1.68)	1.02 (0.52, 2.02)
50+	35 (10.1)	37 (13.9)	13 (12.5)	1.51 (0.88, 2.57)	1.39 (0.66, 2.91)
Ethnicity[d]					
Hispanic	4 (1.2)	5 (1.9)	3 (2.9)	1.00	1.00
Non-Hispanic	341 (98.8)	261 (98.1)	101 (97.1)	0.61 (0.16, 2.30)	0.39 (0.09,1.79)
Race					
Non-White	2 (0.6)	1 (0.4)	0 (0.0)	1.00	1.00
White	344 (99.4)	266 (99.6)	104 (100.0)	1.55 (0.14, 17.15)	1.00
Prior MH dx	127 (36.7)	216 (80.9)	94 (90.4)	**7.30 (5.02, 10.63)**	**16.21 (8.15, 32.24)**
Prior SU dx	222 (64.2)	238 (89.1)	96 (92.3)	**4.58 (2.94, 7.14)**	**6.70 (3.15, 14.25)**
Prior Med dx[e]	100 (28.9)	127 (47.6)	54 (51.9)	**2.23 (1.60, 3.12)**	**2.66 (1.69, 4.16)**
Prior HIV or Hepatitis C dx	29 (8.4)	34 (12.7)	12 (11.5)	1.60 (0.94, 2.69)	1.43 (0.70, 2.90)
Prior Chronic Pain dx	65 (18.8)	77 (28.8)	30 (28.9)	**1.75 (1.20, 2.56)**	**1.75 (1.06, 2.90)**
Prior Buprenorphine medication[f]	167 (50.5)	134 (50.8)	46 (45.1)	1.01 (0.73, 1.40)	0.81 (0.52, 1.26)

[a] Comparing any prior depression to no prior depression

[b] Comparing any past year depression to no prior depression

[c] At the time of first OUD diagnosis

[d] Missing 2 (sample size 611; 449)

[e] Includes hypertensive disease, diabetes mellitus, and other disorders of the airway (i.e. COPD and asthma)

[f] Ordered or dispensed; N=595

Table 3.2 Frequency of each healthcare service outcome after first OUD diagnosis by depression exposure group (N=608)

	OUD wo prior DEP (n=341)	OUD w prior DEP (n=267)	OUD w past year DEP (n=104)	Unadjusted relative risk ratio (RRR)[a] (95% CI)	Unadjusted relative risk ratio (RRR)[b] (95% CI)
Health service outcome	**n (%)**	**n (%)**	**n (%)**		
Emergency Department Encounters					
Zero	183 (53.7)	147 (55.1)	47 (45.2)	1.00	1.00
One	52 (15.3)	43 (16.1)	20 (19.2)	1.03 (0.65, 1.63)	1.49 (0.82, 2.75)
Two or more	106 (31.1)	77 (28.8)	37 (35.6)	0.90 (0.63, 1.30)	1.36 (0.83, 2.22)
Suicide-related					
Zero	327 (95.9)	253 (94.8)	98 (94.2)	1.00	1.00
One	12 (3.5)	7 (2.6)	4 (3.9)	0.75 (0.29, 1.94)	1.11 (0.35, 2.53)
Two or more	2 (0.6)	7 (2.6)	2 (1.9)	4.52 (0.93, 22.0)	3.34 (0.46, 24.00)
Overdose-related					
Zero	323 (94.7)	260 (97.4)	101 (97.1)	1.00	1.00
One	14 (4.1)	5 (1.9)	2 (1.9)	0.44 (0.16, 1.25)	0.46 (0.10, 2.04)
Two or more	4 (1.2)	2 (0.6)	1 (1.0)	0.62 (0.11, 3.42)	0.80 (0.09, 7.23)
MH dx-related[c]					
Zero	276 (80.9)	192 (71.9)	64 (61.5)	1.00	1.00
One	29 (8.5)	36 (13.5)	22 (21.2)	**1.78 (1.06, 3.01)**	**3.27 (1.76, 6.06)**
Two or more	36 (10.6)	39 (14.6)	18 (17.3)	1.56 (0.95, 2.54)	**2.16 (1.15, 4.04)**
SU dx-related					
Zero	210 (61.6)	170 (63.7)	58 (55.8)	1.00	1.00
One	55 (16.1)	36 (13.5)	16 (15.4)	0.81 (0.51, 1.29)	1.05 (0.56, 1.97)
Two or more	76 (22.3)	61 (22.9)	30 (28.9)	0.99 (0.67, 1.47)	1.43 (0.86, 2.39)
MH or SU dx-related[c]					
Zero	204 (59.8)	165 (61.8)	55 (52.9)	1.00	1.00
One	54 (15.8)	37 (13.9)	16 (15.4)	0.85 (0.53, 1.35)	1.10 (0.58, 2.07)
Two or more	83 (24.3)	65 (24.3)	33 (31.7)	0.97 (0.66, 1.42)	1.47 (0.89, 2.43)
Inpatient Encounters					
Zero	226 (66.3)	170 (63.7)	57 (54.8)	1.00	1.00
One	52 (15.3)	41 (15.4)	19 (18.3)	1.04 (0.66,1.65)	1.45 (0.79, 2.64)
Two or more	63 (18.5)	56 (21.0)	28 (26.9)	1.18 (0.78, 1.78)	1.76 (1.04, 3.00)
MH dx-related[c]					
Zero	318 (93.3)	234 (87.6)	88 (84.6)	1.00	1.00
One	14 (4.1)	22 (8.2)	7 (6.7)	**2.14 (1.07, 4.26)**	1.81 (0.71, 4.61)

Two or more	9 (2.6)	11 (4.1)	9 (8.7)	1.66 (0.68, 4.07)	**3.61 (1.39, 9.38)**
SU dx-related					
Zero	304 (89.2)	232 (86.9)	84 (80.8)	1.00	1.00
One	25 (7.3))	22 (8.2)	9 (8.7)	1.15 (0.63, 2.10)	1.30 (0.59, 2.90)
Two or more	12 (3.5)	13 (4.9)	11 (10.6)	1.42 (0.64, 3.17)	**3.32 (1.41, 7.79)**
MH or SU dx-related[c]					
Zero	296 (86.8)	223 (83.5)	82 (78.9)	1.00	1.00
One	30 (8.8)	26 (9.7)	10 (9.6)	1.15 (0.66, 2.00)	1.20 (0.56, 2.56)
Two or more	15 (4.4)	18 (6.7)	12 (11.5)	1.59 (0.79, 2.23)	2.89 (1.30, 6.41)
All Overdose-Related Encounters					
Zero	318 (93.3)	251 (94.0)	98 (94.2)	1.00	1.00
One	15 (4.4)	12 (4.5)	5 (4.8)	1.01 (0.47, 2.20)	1.08 (0.38, 3.05)
Two or more	8 (2.4)	4 (1.5)	1 (1.0)	0.63 (0.19, 2.13)	0.41 (0.05, 3.28)
All Suicide-Related Encounters					
Zero	325 (95.3)	253 (94.8)	98 (94.2)	1.00	1.00
One	13 (3.8)	7 (2.6)	4 (3.9)	0.69 (0.27, 1.76)	1.02 (0.33, 3.20)
Two or more	3 (0.9)	7 (2.6)	2 (1.9)	3.00 (0.77, 11.71)	2.21 (0.36, 12.42)

[a] Comparing any prior depression to no prior depression

[b] Comparing any past year depression to no prior depression

[c] Includes depression code

Table 3.3 Healthcare encounters and hazard ratios with 95% confidence intervals (CI) for comparing incidence of each type of encounter between adults with OUD without prior depression (reference) and OUD with any prior/past year depression

	All Prior Depression				Past Year Depression			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][a]	IPTW adjusted Hazard Ratio [95% CI][b]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][a]	IPTW adjusted Hazard Ratio [95% CI][a,c,d]
ED encounters								
All	1225	2.88	**1.73 [1.20, 2.49]**	1.21 [0.81, 1.80]	937	2.87	**2.26 [1.41, 3.63]**	1.40 [0.87, 2.25]
Reason for ED encounter								
Overdose	34	0.08	1.26 [0.39, 4.11]	1.88 [0.67, 5.28]	28	0.09	0.78 [0.26,2.29]	1.24 [0.05, 34.04]
Suicide	45	0.11	**2.94 [1.43, 6.03]**	**2.80 [1.35, 5.80]**	29	0.09	**8.27 [1.25, 54.87]**	**11.93 [1.56, 91.04]**
Mental illness (MI)[e]	422	0.99	1.62 [0.92, 2.84]	1.13 [0.68, 1.88]	304	0.93	**2.14 [1.23,3.72]**	1.47 [0.94, 2.31]
Substance use (SU)	798	1.88	**2.14 [1.41, 3.23]**	**1.59 [1.04, 2.44]**	599	1.84	**2.88 [1.80,4.59]**	**1.76 [1.11, 2.80]**
MI or SU[e]	897	2.11	**1.95 [1.29, 2.95]**	1.41 [0.88, 2.25]	677	2.07	**2.69 [1.72,4.20]**	**1.70 [1.07, 2.69]**
Inpatient encounters								
All	515	1.21	1.42 [0.72, 2.77]	1.39 [0.72, 2.71]	402	1.23	1.11 [0.43, 2.87]	0.49 [0.23, 1.04]
Reason for inpatient encounter								
Mental illness (MI)[e]	92	0.22	2.11 [0.61, 7.27]	1.64 [0.49, 5.47]	73	0.22	1.26 [0.32, 4.93]	0.61 [0.23, 1.59]
Substance use (SU)	114	0.27	2.08 [0.73, 5.94]	1.62 [0.56, 4.68]	96	0.29	1.69 [0.53,5.40]	0.40 [0.10, 1.68]
MI or SU[e]	147	0.35	1.92 [0.68, 5.47]	1.59 [0.57, 4.42]	118	0.36	1.36 [0.40, 4.68]	0.58 [0.20, 1.66]
Overdose-related								
Any type of encounter for overdose	56	0.13	1.94 [0.80, 4.73]	2.27 [0.99, 5.21]	42	0.13	1.41 [0.50, 3.97]	1.65 [0.18, 15.03]
Suicide-related								
Any type of encounter for suicide	56	0.13	1.77 [0.83, 3.81]	1.73 [0.80, 3.72]	38	0.12	**8.27 [1.25, 54.87]**	3.39 [0.47, 24.40]

[a] Cox proportional hazards model: the Prentice, Williams and Peterson (PWP) used to estimate crude and stabilized IPTW hazard ratios

[b] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered and/or dispensed)

[c] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered and/or dispensed)

[d] Doubly robust with sex, mental health diagnosis other than depression in year prior to first OUD diagnosis, substance use diagnosis other than OUD in year prior to first OUD dx and buprenorphine prescription in year prior to first OUD dx included in both the propensity score weight and regression model

[e] Includes depression

Supplemental Table 3.1 ICD 9 and ICD 10 codes used to define diagnoses

Diagnosis categories	Diagnosis Included
Mental health and Substance use	
Opioid use disorder	ICD9: 304, 304.0, 304.00-.02, 305.5, 305.50-.52 ICD10: F11, F11.1, F11.10, F11.12, F11.120-.122, F11.129, F11.14, F11.15, F11.150-.151, F11.159, F11.18, F11.181-.182, F11.188, F11.19, F11.2, F11.20, F11.22, F11.220-.222", F11.229, F11.23-.25, F11.250-.251, F11.259, F11.28, F11.281-.282, F11.288, F11.29, F11.9, F11.90, F11.92, F11.920-.922, F11.929, F11.93-.95, F11.950-.951, F11.959, F11.98, F11.981-.982, F11.988, F11.99
Depressive disorders	ICD9: 296.2*, 296.3*, 300.4*, 311 ICD10: F32*, F33*, F34.1
Other substance use disorder	ICD9: 303*, 304.1*, 304.2*, 304.3*, 304.4*, 304.5*, 304.6*, 304.8*, 304.9*, 305.0*, 305.1*,305.2*, 305.3*, 305.4*, 305.6*, 305.7*, 305.9* ICD10: F10*, F12*-F19*, F55*
Other mental health disorder	ICD9: 290*-296*, 297*-299*, 300*, 301*, 302*, 308*, 309* ICD10: F01*-F09*, F20*-F25*, F28*-F29*, F31*, F34*, F39, F40*, F41.0, F41.1, F41.3, F41.8, F41.9, F42*-F45*, F48*, F50*-F52*, F54*, F59*, F60*, F63*-F69*, F99*
Suicide attempt	ICD9: E950*-E958* ICD10: T14.91*, X71*-X83*
Suicide ideation	ICD9: V62.84 ICD10: R45.851
Overdose	
Opioid overdose	ICD9: 965, 965.0, 965.01, 965.09, E850.0, E850.2 ICD10: T40.0X1*, T40.0X2*, T40.0X4*, T40.1-.4*, T40.6*
Other drug overdose	ICD9: 965.1, 965.4, 965.5, 965.6*, 965.7-.9, 967*, 968*, 969*, 969.4, 970*, 970.81 980*, 981, 982*, E850.3-.9, E851, E852*, E853*, E854*, E855.1, E858.8-.9, E860*, E862*, E980*, E980.0-.5 ICD10: T39.011*, T39.012*, T39.014*, T39.091*, T39.092*, T39.094*, T39.4X1*, T39.4X2*, T39.4X4*, T39.8X1*, T39.8X2*, T39.8X4*, T39.91*, T39.92*, T39.94*, T40.5X1*, T40.5X2*, T40.5X4*, T40.7X1*, T40.7X2*, T40.7X4*, T40.8X1*, T40.8X2*, T40.8X4*, T40.901*, T40.902*, T40.904*, T40.991*, T40.992*, T40.994*, T41.0X1*, T41.0X2*, T41.0X4*, T41.1X1*, T41.1X2*, T41.1X4*, T41.201*, T41.202*, T41.204*, T41.291*, T41.292*, T41.294*, T41.3X1*, T41.3X2*, T41.3X4*, T41.41*, T41.42*, T41.44*, T42.3X1*, T42.3X2*, T42.3X4*, T42.4X1*, T42.4X2*, T42.4X4*, T43.601*, T43.602*, T43.604*, T43.621*, T43.622*, T43.624*, T43.631*, T43.632*, T43.634*, T43.641*, T43.642*, T43.644*, T43.691*, T43.692*, T43.694*, T43.8X1*, T43.8X2*, T43.8X4*, T43.91*, T43.92*, T43.94*
Other medical	
Chronic pain	ICD9: 338.2*, 338.4, ICD10: G89.2*, G89.4
HIV and Hepatitis C	ICD9: 042, 070.41, 070.44, 070.51, 070.54, 070.71 ICD10: B20, B17.1*, B18.2, B19.2*
Other *(includes hypertensive disease, diabetes mellitus, disorders of the airway-COPD and asthma)*	ICD9: 401*-405*, 205*, 490*-496* ICD10: I10*-I13*, I15*-I16*, E08*-E11*, E13*, J40*-J45*, J47*

Supplemental Table 3.2 Proportions for each covariate and standardized differences comparing opioid use disorder without any prior depression and opioid use disorder with any prior depression before and after weighting for all prior diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis

	Crude (Unweighted)				Weighted (stabilized)[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=267)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=330)	OUD w prior DEP (n=263)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	34.5	3.4	-0.071	37.5	37.8	0.3	0.006
30-39	36.1	36.7	0.6	0.012	35.9	35.4	0.5	-0.009
40-49	15.9	15.0	0.9	-0.025	15.0	16.0	1.0	0.028
50+	10.1	13.9	3.8	0.115	11.7	10.8	0.9	-0.027
Male sex	59.5	39.7	19.8	-0.404	49.0	48.2	0.8	-0.017
Non-Hispanic Ethnicity	98.8	98.1	0.7	-0.059	98.0	97.6	0.4	-0.031
White race	99.4	99.6	0.2	0.030	99.5	99.6	0.1	0.013
Prior MH dx	36.7	80.9	44.2	1.003	57.5	58.3	0.8	0.016
Prior SU dx[a]	64.2	89.1	24.9	0.617	76.1	77.3	1.2	0.030
Prior Med dx[a]	28.9	47.6	18.7	0.391	37.2	37.9	0.7	0.015
Prior HIV/ Hep C dx[a]	8.4	12.7	4.3	0.142	11.8	11.4	0.4	-0.013
Prior chronic pain dx[a]	18.8	28.8	10.0	0.237	24.9	25.8	0.9	0.021
Prior bup med [a,b]	50.5	50.8	0.3	0.006	50.4	53.8	3.4	0.068

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Includes past ordered or dispensed buprenorphine medications; Unweighted sample sizes: OUD without prior DEP n=331, OUD with prior DEP n=264; Weighted sample sizes: OUD without prior DEP n=330, OUD with prior DEP n=263

[c] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered and/or dispensed)

Supplemental Table 3.3 Proportions for each covariate and standardized differences comparing opioid use disorder without past year depression and opioid use disorder with past year depression before and after weighting for all past year diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis

	Crude (Unweighted)				Weighted (stabilized)[d]			
	OUD wo past year DEP (n=346)	OUD w past year DEP (n=104)	Difference in proportions	Standardized differences	OUD wo past year DEP (n=328)	OUD w past year DEP (n=102)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	33.7	4.2	-0.088	35.8	40.4	4.6	0.096
30-39	36.1	39.4	3.3	0.068	39.1	38.9	0.2	-0.005
40-49	15.9	14.4	1.5	-0.041	14.2	7.9	6.3	-0.175
50+	10.1	12.5	2.4	0.075	10.8	12.8	2.0	0.061
Male sex	59.5	43.3	16.2	-0.329	53.9	39.3	14.6	-0.296
Non-Hispanic Ethnicity	98.8	97.1	1.7	-0.122	98.6	98.3	0.3	-0.023
White race	99.4	100.0	0.6	0.108	100.0	100.0	0.0	0.000
Prior year MH dx[b]	14.5	74.0	59.5	1.494	30.8	36.9	6.1	0.154
Prior year SU dx[b]	28.9	73.1	44.2	0.982	41.9	48.4	6.5	0.145
Prior year Med dx[b]	12.1	40.4	28.3	0.675	20.9	24.8	3.9	0.095
Prior year HIV/ Hep C dx[b]	1.4	5.8	4.4	0.233	1.9	3.2	1.3	0.070
Prior year chronic pain dx[b]	6.1	21.2	15.1	0.449	9.3	10.9	1.6	0.049
Prior year bup med[b,c]	46.5	39.2	7.3	-0.148	44.0	38.1	5.9	-0.120

[a] OUD without past year DEP= no depression OR depression on/after first OUD dx (n=346); OUD with past year DEP =had at least one depression code within year prior to first OUD dx (n=104); patients that had a depression code more than a year prior to first OUD dx and did not have another were excluded (n=163)

[b] The definition of all of these DO NOT include the day of OUD dx (e.g. within 1 year prior to first OUD dx date)

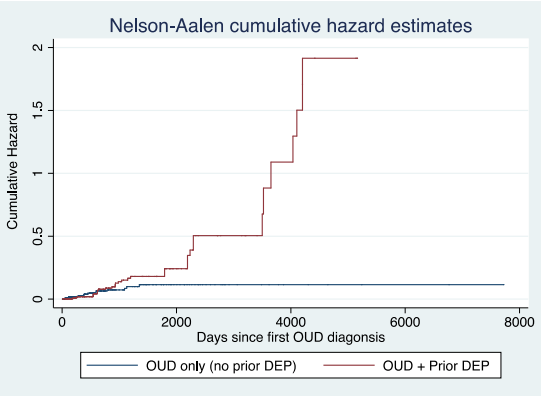
[c] Includes past ordered or dispensed buprenorphine medications; Unweighted sample sizes: OUD without prior DEP n=331, OUD with prior DEP n=102; Weighted sample sizes: OUD without prior DEP n=328, OUD with prior DEP n=102

[d] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior year MI dx, prior year SUD dx, prior year Medical dx, prior year HIV or Hep C dx, prior year chronic pain dx, prior year buprenorphine prescription (ordered and/or dispensed)

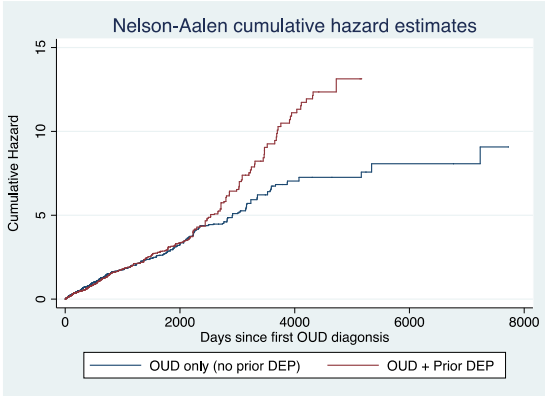
Supplemental Figure 3.1 Weighted cumulative hazard plots for A) all prior depression B) past year depression

A) All prior depression

A.1. Suicide-related ED visits

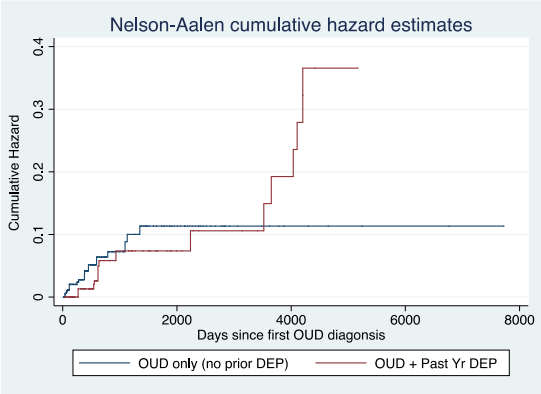


A.2. Substance use-related ED visits

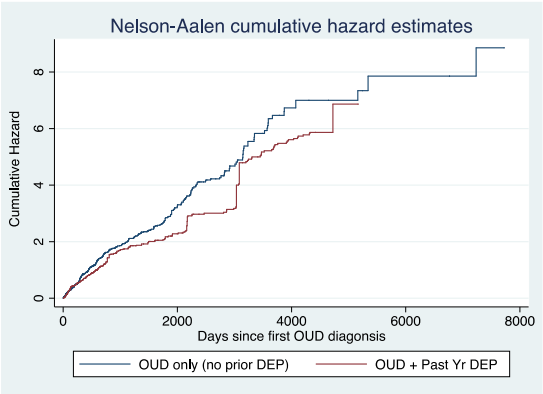


B) Past year depression

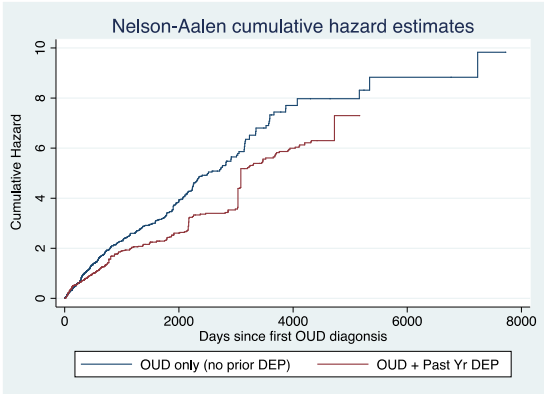
B.1. Suicide-related ED visits



B.2. Substance use-related ED visits



B.2. Substance use or mental health-related ED visits



Chapter 3 Appendices

3.1 Frequency of each healthcare service outcome before and after first OUD diagnosis

	After OUD dx[a]	Before OUD dx[a]	Total
Total number of encounters	21,058	31,125	52,183
Emergency Department Encounters			
All	1,225	3,976	5,201
Overdose-related	34	77	111
Suicide-related	45	85	130
MH dx-related	422	628	1,050
SU dx-related	798	1,204	2,002
MH or SU dx-related	897	1,429	2,326
Inpatient Encounters			
All	515	975	1,490
MH dx-related	92	184	276
SU dx-related	114	219	333
MH or SU dx-related	147	295	442
All Overdose-Related Encounters	56	111	167
All Suicide-Related Encounters	56	110	166

[a] First OUD dx in EHR

3.2 Comparing days to exit: 1) from first GHS encounter date; 2) from first OUD dx date

	Mean Days to Exit (SD)	Range
From first encounter	5669.3 (1792.7)	530, 8425
From OUD origin	872.4 (917.4)	0, 7724

3.3 Differences in length of observation prior to first OUD diagnosis between depression groups

	No prior depression		All prior depression		Past year depression	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Days to first OUD dx	2984.2 (2357.2)	0,8127	4674.9 (1968.8)	34,8328	4272.2 (2182.1)	34,8216

*t-tests significant at $p<0.001$

3.4 Sample characteristics by depression exposure group- All prior depression and no exclusion based on observation length between first GHS encounter and first OUD diagnosis

	OUD wo prior DEP (n=447) n (%)	OUD w prior DEP (n=274) n (%)	Unadjusted Odds Ratio (95% CI)
Sex			
Female	179 (40.0)	164 (59.9)	1.00
Male	268 (60.0)	110 (40.2)	**0.45 (0.33, 0.61)**
Age group[a]			
18-29	169 (37.8)	95 (36.7)	1.00
30-39	165 (36.9)	95 (34.7)	1.08 (0.76, 1.54)
40-49	69 (15.4)	42 (15.3)	1.08 (0.68, 1.71)
50+	44 (9.8)	37 (13.5)	1.50 (0.90, 2.48)
Ethnicity			
Hispanic	13 (2.9)	5 (1.8)	1.00
Non-Hispanic	433 (97.1)	268 (98.2)	1.61 (0.57, 4.56)
Race			
Non-White	6 (1.3)	1 (0.4)	1.00
White	441 (98.7)	273 (99.6)	3.71 (0.44, 31.01)
Prior MH dx	136 (30.4)	219 (79.9)	**9.12 (6.37, 13.02)**
Prior SU dx	238 (53.2)	242 (88.3)	**6.64 (4.39, 10.04)**
Prior Med dx[b]	106 (23.7)	128 (46.7)	**2.82 (2.04, 3.89)**
Prior HIV or Hepatitis C dx	30 (6.7)	34 (12.4)	**1.97 (1.18, 3.30)**
Prior Chronic Pain dx	65 (14.5)	78 (28.5)	**2.34 (1.61, 3.39)**
Prior Buprenorphine medication[c]	215 (50.7)	136 (50.2)	0.98 (0.72, 1.33)

[a] At the time of first OUD diagnosis

[b] Includes hypertensive disease, diabetes mellitus, and other disorders of the airway (i.e. COPD and asthma)

[c] Ordered or dispensed

3.5 Frequency of each healthcare service outcome by depression exposure group- All prior depression and no exclusion based on observation length between first GHS encounter and first OUD diagnosis

	OUD wo prior DEP (n=447)	OUD w prior DEP (n=274)
Health service outcome	**n (%)**	**n (%)**
Emergency Department Encounters[a]		
All	190 (42.5)	122 (44.5)
One	66 (34.7)	45 (36.9)
Two or more	124 (65.3)	77 (63.1)
Overdose-related	20 (4.5)	7 (2.6)
One	15 (75.0)	5 (71.4)
Two or more	5 (25.0)	2 (28.6)
Suicide-related	16 (3.6)	14 (5.1)
One	14 (87.5)	7 (50.0)
Two or more	2 (12.5)	7 (50.0)
MH dx-related[b]	77(17.2)	75 (27.4)
One	37 (48.1)	36 (48.0)
Two or more	40 (51.9)	39 (52.0)
SU dx-related	158 (35.3)	97 (35.4)
One	69 (43.7)	36 (37.1)
Two or more	89 (56.3)	61 (62.9)
MH or SU dx-related[b]	166 (37.1)	102 (37.2)
One	69 (41.6)	37 (36.3)
Two or more	97 (58.4)	65 (63.7)
Inpatient Encounters[a]		
All	131 (29.3)	98 (35.8)
One	57 (43.5)	42 (42.9)
Two or more	74 (56.5)	56 (57.1)
MH dx-related[b]	24 (5.4)	33 (12.0)
One	15 (62.5)	22 (66.7)
Two or more	9 (37.5)	11 (33.3)
SU dx-related	42 (9.4)	35 (12.8)
One	29 (69.0)	22 (62.9)
Two or more	13 (31.0)	13 (37.1)
MH or SU dx-related[b]	50 (11.2)	44 (16.1)

One	33 (66.0)	26 (59.1)
Two or more	17 (34.0)	18 (40.9)
All Overdose-Related Encounters[a]	26 (5.8)	16 (5.8)
One	17 (65.4)	12 (75.0)
Two or more	9 (34.6)	4 (25.0)
All Suicide-Related Encounters[a]	18 (4.0)	14 (5.1)
One	15 (83.3)	7 (50.0)
Two or more	3 (16.7)	7 (50.0)

3.6 Sample characteristics by the following depression groups: 1) OUD only; 2) OUD+ Prior DEP; 3) OUD + Post DEP (N=721)- No exclusion based on observation length between first GHS encounter and first OUD diagnosis

	OUD only (n=367)	OUD + Prior DEP (n=274)	OUD + Post DEP (n=80)[a]
	n (%)	n (%)	n (%)
Sex			
Female	144 (39.2)	164 (59.9)	35 (43.8)
Male	223 (60.8)	110 (40.2)	45 (56.3)
Age group[b]			
18-29	133 (36.2)	95 (36.7)	36 (45.0)
30-39	143 (39.0)	95 (34.7)	22 (27.5)
40-49	54 (14.7)	42 (15.3)	15 (18.8)
50+	37 (10.9)	37 (13.5)	7 (8.7)
Ethnicity			
Hispanic	12 (3.3)	5 (1.8)	1 (1.3)
Non-Hispanic	354 (96.7)	268 (98.2)	79 (98.7)
Race			
Non-White	4 (1.1)	1 (0.4)	2 (2.5)
White	363 (98.9)	273 (99.6)	78 (97.5)
Prior MH dx	103 (28.1)	219 (79.9)	33 (41.3)
Prior SU dx	188 (51.2)	242 (88.3)	50 (62.5)
Prior Med dx[c]	81 (22.1)	128 (46.7)	25 (31.3)
Prior HIV or Hepatitis C dx	26 (7.1)	34 (12.4)	4 (5.0)
Prior Chronic Pain dx	56 (15.3)	78 (28.5)	9 (11.3)
Prior Buprenorphine medication[d]	186 (53.8)	136 (50.2)	29 (37.2)

[a] 23 patients had first date of OUD and first date of DEP on the same day

[b] At the time of first OUD diagnosis

[c] Includes hypertensive disease, diabetes mellitus, and other disorders of the airway (i.e. COPD and asthma)

[d] Ordered or dispensed

3.7 Healthcare encounters and hazard ratios with 95% confidence intervals (CI) for comparing incidence of each type of encounter between adults with OUD without prior depression (reference) and OUD with *any prior* depression- No exclusion based on observation length between first GHS encounter and first OUD diagnosis

	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][a]	IPTW adjusted Hazard Ratio [95% CI][b]	IPTW adjusted Hazard Ratio [95% CI][c]
ED encounters						
All	1339	2.73	**1.98 [1.40, 2.81]**	1.41 [0.95, 2.08]	1.41 [0.86, 2.29]	**1.66 [1.15, 2.39]**
Reason for ED encounter						
Overdose	37	0.08	1.26 [0.40, 4.11]	2.02 [0.71, 5.70]	2.12 [0.75, 6.02]	1.85 [0.59, 5.76]
Suicide	47	0.10	**3.37 [1.66, 6.88]**	**3.33 [1.58, 7.04]**	**2.75 [1.41, 5.35]**	**2.84 [1.39, 5.79]**
Mental illness (MI)[d]	444	0.90	**1.73 [1.05, 2.86]**	1.21 [0.75, 1.96]	1.15 [0.69,1.93]	1.34 [0.82, 2.21]
Substance use (SU)	861	1.75	**2.25 [1.54, 3.30]**	**1.68 [1.12, 2.53]**	1.57 [0.97, 2.55]	**1.83 [1.22, 2.75]**
MI or SU[d]	968	1.97	**2.05 [1.40, 3.00]**	1.49 [0.95, 2.34]	1.32 [0.73, 2.41]	**1.64 [1.07, 2.50]**
Inpatient encounters						
All	549	1.12	1.40 [0.73, 2.66]	1.42 [0.74, 2.72]	1.34 [0.70, 2.58]	1.17 [0.60, 2.28]
Reason for inpatient encounter						
Mental illness (MI)	93	0.19	2.11 [0.61, 7.27]	1.68 [0.50, 5.70]	1.82 [0.53, 6.31]	1.47 [0.41, 5.29]
Substance use (SU)	121	0.25	2.00 [0.72, 5.56]	1.57 [0.54, 4.60]	1.63 [0.54, 4.86]	1.49 [0.52, 4.30]
MI or SU[d]	155	0.32	1.89 [0.68, 5.23]	1.58 [0.56, 4.45]	1.64 [0.57, 4.77]	1.43 [0.49, 4.18]
Overdose-related						
Any type of encounter for overdose	60	0.12	1.94 [0.80, 4.72]	**2.39 [1.04, 5.50]**	**2.48 [1.09, 5.65]**	2.29 [0.95, 5.52]
Suicide-related						
Any type of encounter for suicide	58	0.12	2.02 [0.95, 4.28]	2.00 [0.90, 4.44]	1.79 [0.89, 3.63]	1.90 [0.94, 3.82]

[a] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered and/or dispensed)

[b] Excludes prior mental health

[c] Excludes prior mental health and substance use disorder codes

[d] Includes depression

3.8 Hazard ratios 1) Truncating follow-up time at 10 years; 2) Excluding depression episodes that occur after OUD dx; 3) Excluding depression from MI outcomes for *any prior* depression

	Truncated at 10 years		Excluding depression episodes post OUD	
	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI]	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI]
ED encounters				
All	**1.68 [1.16, 2.44]**	1.18 [0.79, 1.76]	**1.85 [1.27, 2.68]**	1.34 [0.91, 1.96]
Reason for ED encounter				
Overdose	1.26 [0.39,4.11]	1.88 [0.67,5.28]	1.35 [0.28, 6.47]	1.85 [0.59, 5.79]
Suicide	**2.94 [1.43,6.03]**	**2.80 [1.36, 5.80]**	**2.90 [1.18, 7.11]**	2.34 [0.91, 6.06]
Mental illness (MI)[a]	1.52 [0.85, 2.71]	1.08 [0.64,1.80]	**1.42 [0.77, 2.63]**	1.17 [0.66, 2.08]
Substance use (SU)	**2.07 [1.37, 3.14]**	**1.55 [1.01, 2.38]**	**2.07 [1.34, 3.19]**	**1.58 [1.02, 2.46]**
MI or SU[a]	**1.89 [1.25, 2.85]**	1.37 [0.86, 2.19]	**1.99 [1.30, 3.04]**	1.49 [0.93, 2.39]
Inpatient encounters				
All	1.42 [0.72, 2.77]	1.39 [0.72, 2.71]	1.52 [0.88, 2.62]	1.56 [0.87, 2.80]
Reason for inpatient encounter				
Mental illness (MI)[a]	2.11 [0.61, 7.27]	1.64 [0.49, 5.47]	**4.59 [1.70, 12.40]**	**3.53 [1.31, 9.51]**
Substance use (SU)	2.08 [0.73, 5.94]	1.62 [0.56, 4.68]	2.23 [0.81, 6.13]	1.61 [0.59, 4.37]
MI or SU[a]	1.92 [0.68, 5.47]	1.59 [0.57, 4.42]	2.48 [0.97, 6.34]	1.93 [0.78, 4.79]
Overdose-related				
Any type of encounter for overdose	1.94 [0.80, 4.73]	2.27 [0.99, 5.21]	2.31 [0.87, 6.12]	**2.56 [1.12, 5.84]**
Suicide-related				
Any type of encounter for suicide	1.77 [0.83, 3.81]	1.73 [0.80, 3.72]	**3.08 [1.20, 7.93]**	2.46 [0.94, 6.48]

[b] Includes depression

Excluding depression from MI outcomes		
	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI]
ED encounters		
All	**1.73 [1.20, 2.49]**	1.21 [0.81, 1.80]
Reason for ED encounter		
Overdose	1.26 [0.39, 4.11]	1.88 [0.67, 5.28]
Suicide	**2.94 [1.43, 6.03]**	**2.80 [1.35, 5.80]**
Mental illness (MI) (excluding dep)	1.19 [0.67, 2.11]	0.93 [0.52, 1.66]
Substance use (SU)	**2.14 [1.41, 3.23]**	**1.59 [1.04, 2.44]**
MI or SU (excluding dep)	**1.97 [1.31, 2.96]**	1.46 [0.93, 2.31]
Inpatient encounters		

All	1.42 [0.72, 2.77]	1.39 [0.72, 2.71]
Reason for inpatient encounter		
Mental illness (MI) (excluding dep)	1.32 [0.33, 5.29]	1.07 [0.29, 3.98]
Substance use (SU)	2.08 [0.73, 5.94]	1.62 [0.56, 4.68]
MI or SU (excluding dep)	1.83 [0.62, 5.40]	1.50 [0.51, 4.36]
Overdose-related		
Any type of encounter for overdose	1.94 [0.80, 4.73]	2.27 [0.99, 5.21]
Suicide-related		
Any type of encounter for suicide	1.77 [0.83, 3.81]	1.73 [0.80, 3.72]

3.9 Hazard ratios 1) Truncating follow-up time at 10 years; 2) Excluding depression episodes that occur after OUD dx; 3) Excluding depression from MI outcomes for *past year* depression

	Truncated at 10 years		**Excluding depression episodes post OUD**	
	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][a]	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][a]
ED encounters				
All	**2.21 [1.36, 3.58]**	1.34 [0.71, 2.54]	**2.41 [1.45, 3.93]**	1.58 [0.90, 2.78]
Reason for ED encounter				
Overdose	0.78 [0.26, 2.29]	2.36 [0.19, 30.08]	0.46 [0.06, 3.33]	0.71 [0.10, 4.92]
Suicide	**8.27 [1.25, 54.87]**	8.17 [0.95, 69.58]	6.04 [0.87, 42.04]	**8.08 [1.40, 46.51]**
Mental illness (MI)[b]	**1.98 [1.10, 3.58]**	1.53 [0.95, 2.47]	1.83 [0.94, 3.58]	1.48 [0.90, 2.43]
Substance use (SU)	**2.78 [1.72, 4.48]**	**2.13 [1.38, 3.31]**	**2.71 [1.62, 4.51]**	**2.12 [1.31, 3.43]**
MI or SU[b]	**2.59 [1.64, 4.10]**	**2.06 [1.35, 3.14]**	**2.69 [1.67, 4.35]**	**2.22 [1.41, 3.51]**
Inpatient encounters				
All	1.11 [0.43, 2.87]	0.46 [0.15, 1.40]	1.19 [0.55, 2.60]	0.59 [0.22, 1.57]
Reason for inpatient encounter				
Mental illness (MI)[b]	1.26 [0.32, 4.93]	0.28 [0.05, 1.61]	2.58 [0.97, 6.82]	1.02 [0.26, 4.01]
Substance use (SU)	1.69 [0.53, 5.40]	0.42 [0.07, 2.56]	1.79 [0.60, 5.35]	0.49 [0.08, 2.82]
MI or SU[b]	1.36 [0.40, 4.68]	0.35 [0.07, 1.78]	1.72 [0.59, 4.98]	0.51 [0.10, 2.50]
Overdose-related				
Any type of encounter for overdose	1.41 [0.50, 3.97]	1.01 [0.16, 6.53]	1.56 [0.48, 5.04]	0.87 [0.09, 7.19]
Suicide-related				
Any type of encounter for suicide	8.27 [1.25, 54.87]	7.85 [0.81, 76.21]	6.04 [0.87, 42.04]	8.08 [1.40, 46.51]

[a] Regression model includes sex

[b] Includes depression

Excluding depression from MI outcomes[a]		
	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][a]
ED encounters		
All	**2.26 [1.41, 3.63]**	1.37 [0.73, 2.58]
Reason for ED encounter		
Overdose	0.78 [0.26,2.29]	2.36 [0.19, 30.08]
Suicide	**8.27 [1.25,54.87]**	**8.14 [0.95, 69.58]**
Mental illness (MI) (excluding dep)	**1.85 [1.05, 3.25]**	1.45 [0.83, 2.54]
Substance use (SU)	**2.88 [1.80,4.59]**	**2.21 [1.44, 3.40]**
MI or SU (excluding dep)	**2.66 [1.68, 4.20]**	2.08 [1.38, 3.15]
Inpatient encounters		
All	1.11 [0.43, 2.87]	0.46 [0.15, 1.40]
Reason for inpatient encounter		
Mental illness (MI) (excluding dep)	0.79 [0.18, 3.54]	**0.14 [0.03, 0.72]**
Substance use (SU)	1.69 [0.53,5.40]	0.42 [0.07, 2.56]
MI or SU (excluding dep)	1.31 [0.38, 4.50]	0.34 [0.07, 1.75]
Overdose-related		
Any type of encounter for overdose	1.41 [0.50, 3.97]	1.01 [0.16, 6.53]
Suicide-related		
Any type of encounter for suicide	**8.27 [1.25, 54.87]**	7.85 [0.81, 76.21]

[a] Regression model includes sex

3.10 Healthcare encounters and hazard ratios with 95% confidence intervals (CI) for comparing incidence of each type of encounter between adults with OUD without prior depression (reference) and OUD with any prior/past year depression:[a] Limited propensity score models

	All Prior Depression				Past Year Depression			
	Number of events	Incidence rate per 1000 person-years	IPTW adjusted Hazard Ratio [95% CI][b]	IPTW adjusted Hazard Ratio [95% CI][c]	Number of events	Incidence rate per 1000 person-years	IPTW adjusted Hazard Ratio [95% CI][b]	IPTW adjusted Hazard Ratio [95% CI][c]
ED encounters								
All	1225	2.88	1.29 [0.81, 2.07]	**1.50 [1.03, 2.20]**	937	2.87	1.46 [0.82, 2.59]	1.83 [1.16, 2.90]
Reason for ED encounter								
Overdose	34	0.08	1.98 [0.70, 5.63]	1.77 [0.56, 5.58]	28	0.09	1.17 [0.37, 3.66]	0.95 [0.30, 2.97]
Suicide	45	0.11	**2.39 [1.25, 4.55]**	**2.57 [1.27, 5.22]**	29	0.09	7.52 [0.65, 87.02]	7.35 [0.80, 67.30]
Mental illness (MI)[d]	422	0.99	1.12 [0.66,1.92]	1.31 [0.76, 2.24]	304	0.93	1.29 [0.71, 2.34]	1.64 [0.95, 2.81]
Substance use (SU)	798	1.88	1.57 [0.96, 2.55]	**1.82 [1.18, 2.79]**	599	1.84	**2.12 [1.33, 3.39]**	**2.54 [1.68, 3.85]**
MI or SU[d]	897	2.11	1.33 [0.75, 2.39]	**1.63 [1.05, 2.55]**	677	2.07	**1.98 [1.25, 3.14]**	**2.31 [1.54, 3.46]**
Inpatient encounters								
All	515	1.21	1.33 [0.69, 2.59]	1.22 [0.62, 2.40]	402	1.23	1.06 [0.42, 2.71]	0.88 [0.30, 2.56]
Reason for inpatient encounter								
Mental illness (MI)	92	0.22	1.79 [0.52, 6.14]	1.54 [0.44, 5.42]	73	0.22	1.08 [0.24, 4.91]	0.82 [0.17, 4.04]
Substance use (SU)	114	0.27	1.66 [0.56, 4.94]	1.59 [0.55, 4.60]	96	0.29	1.45 [0.37, 5.66]	1.26 [0.34, 4.67]
MI or SU[d]	147	0.35	1.64 [0.57, 4.75]	1.50 [0.52, 4.36]	118	0.36	1.20 [0.30, 4.89]	1.00 [0.25, 4.03]
Overdose-related								
Any type of encounter for overdose	56	0.13	**2.34 [1.02, 5.37]**	2.20 [0.91, 5.53]	42	0.13	1.56 [0.59, 4.10]	1.50 [0.53, 4.18]
Suicide-related								
Any type of encounter for suicide	56	0.13	1.58 [0.79, 3.17]	1.70 [0.84, 3.44]	38	0.12	7.52 [0.65, 87.02]	7.36 [0.80, 67.30]

[a] Limited to patients with at least one year of observation prior to first opioid use disorder diagnosis
[b] IPTW excludes prior mental health
[c] IPTW excludes prior mental health and substance use disorder codes
[d] Includes depression

3.11 Healthcare encounters and hazard ratios with 95% confidence intervals (CI) for comparing incidence of each type of encounter between adults with OUD without prior depression (reference) and OUD with any prior/past year depression:[a] Missing indicator IPTW

	All Prior Depression			Past Year Depression		
	Number of events	Incidence rate per 1000 person-years	IPTW adjusted Hazard Ratio [95% CI][b]	Number of events	Incidence rate per 1000 person-years	IPTW adjusted Hazard Ratio [95% CI][b,c]
ED encounters						
All	1225	2.86	1.16 [0.80, 1.73]	930	2.85	1.29 [0.70, 2.37]
Reason for ED encounter						
Overdose	34	0.09	1.82 [0.73, 4.54]	27	0.08	2.32 [0.18, 29.63]
Suicide	45	0.09	**2.86 [1.38, 5.93]**	29	0.06	8.41 [0.97, 73.16]
Mental illness[d]	422	1.01	1.14 [0.68,1.88]	303	1.00	1.61 [1.01, 2.55]
Substance use	798	1.84	1.45 [0.95, 2.31]	594	1.71	**1.87 [1.12, 3.10]**
MI or SU[d]	897	2.12	1.33 [0.83, 2.12]	672	2.00	**1.84 [1.14, 2.97]**
Inpatient encounters						
All	515	1.22	1.39 [0.71, 2.70]	398	1.22	0.44 [0.15, 1.34]
Reason for inpatient encounter						
Mental illness[d]	92	0.20	1.64 [0.49, 5.47]	73	0.20	0.25 [0.04, 1.40]
Substance use	114	0.23	1.59 [0.55, 4.58]	96	0.22	0.35 [0.06, 2.13]
MI or SU[d]	147	0.31	1.56 [0.56, 4.36]	118	0.31	0.31 [0.06, 1.55]
Overdose-related						
Any type of encounter for overdose	56	0.15	**2.24 [1.01, 4.96]**	41	0.13	1.00 [0.15, 6.52]
Suicide-related						
Any type of encounter for suicide	56	0.11	1.75 [0.80, 3.82]	38	0.09	8.07 [0.82, 79.04]

[a] Limited to patients with at least one year of observation prior to first opioid use disorder diagnosis
[b] IPTW includes missing data indicator for prior/past year buprenorphine prescriptions
[c] Regression model includes sex
[d] Includes depression

3.12 Proportions of covariates and standardized differences for all prior depression limited to patients with at least a year of observation prior to first OUD diagnosis with a) excluding prior mental illness diagnoses from IPTW; b) excluding prior mental illness and substance use disorder diagnoses from IPTW

a. All prior depression: excluding prior mental illness from propensity score model and IPTW

	Crude (Unweighted)				Weighted (stabilized)[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=267)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=330)	OUD w prior DEP (n=263)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	34.5	3.4	-0.071	36.9	37.7	0.8	0.018
30-39	36.1	36.7	0.6	0.012	36.2	36.8	0.6	0.012
40-49	15.9	15.0	0.9	-0.025	15.4	14.7	0.7	-0.020
50+	10.1	13.9	3.8	0.115	11.5	10.7	0.8	-0.022
Male sex	59.5	39.7	19.8	-0.404	49.1	48.8	0.3	-0.006
Non-Hispanic Ethnicity	98.8	98.1	0.7	-0.059	97.8	98.2	0.4	0.036
White race	99.4	99.6	0.2	0.030	99.5	99.6	0.1	0.010
Prior SU dx[a]	64.2	89.1	24.9	0.617	76.1	77.5	1.4	0.035
Prior Med dx[a]	28.9	47.6	18.7	0.391	38.3	37.9	0.4	-0.008
Prior HIV/ Hep C dx[a]	8.4	12.7	4.3	0.142	11.7	11.7	0.0	0.001
Prior chronic pain dx[a]	18.8	28.8	10.0	0.237	24.2	24.3	0.1	0.001
Prior bup med [a,b]	50.5	50.8	0.3	0.006	50.7	50.4	0.3	-0.005

b. All prior depression: excluding prior mental illness and substance use disorders from propensity score model and IPTW

	Crude (Unweighted)				Weighted (stabilized)[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=267)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=330)	OUD w prior DEP (n=263)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	34.5	3.4	-0.071	36.7	36.4	0.3	-0.006
30-39	36.1	36.7	0.6	0.012	35.9	36.5	0.6	0.010
40-49	15.9	15.0	0.9	-0.025	15.8	15.8	0.0	-0.002
50+	10.1	13.9	3.8	0.115	11.5	11.4	0.1	-0.004
Male sex	59.5	39.7	19.8	-0.404	49.7	49.9	0.2	0.005
Non-Hispanic Ethnicity	98.8	98.1	0.7	-0.059	98.1	98.4	0.3	0.020
White race	99.4	99.6	0.2	0.030	99.5	99.6	0.1	0.013
Prior Med dx[a]	28.9	47.6	18.7	0.391	37.9	37.6	0.3	-0.006
Prior HIV/ Hep C dx[a]	8.4	12.7	4.3	0.142	11.2	11.2	0.0	-0.000

Prior chronic pain dx[a]	18.8	28.8	10.0	0.237	23.4	23.0	0.4	-0.009
Prior bup med [a,b]	50.5	50.8	0.3	0.006	50.9	50.8	0.1	-0.002

c. All prior depression: with IPTW including missing indicator variable for buprenorphine medications

	Crude (Unweighted)				Weighted (stabilized) w missing[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=267)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=345)	OUD w prior DEP (n=266)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	34.5	3.4	-0.071	36.9	36.9	0.0	0.001
30-39	36.1	36.7	0.6	0.012	36.2	35.9	0.3	-0.005
40-49	15.9	15.0	0.9	-0.025	15.4	16.3	0.9	0.027
50+	10.1	13.9	3.8	0.115	11.5	10.8	0.7	-0.024
Male sex	59.5	39.7	19.8	-0.404	49.9	49.4	0.5	-0.011
Non-Hispanic Ethnicity	98.8	98.1	0.7	-0.059	98.0	97.7	0.3	-0.031
White race	99.4	99.6	0.2	0.030	99.6	99.6	0.0	0.013
Prior MH dx[a]	36.7	80.9	44.2	1.003	56.3	57.3	1.0	0.022
Prior SU dx[a]	64.2	89.1	24.9	0.617	75.7	77.9	2.2	0.052
Prior Med dx[a]	28.9	47.6	18.7	0.391	40.0	38.0	2.0	0.022
Prior HIV or Hep C dx[a]	8.4	12.7	4.3	0.142	11.8	11.7	0.1	-0.005
Prior Chronic Pain dx[a]	18.8	28.8	10.0	0.237	25.0	26.2	1.2	0.029
Prior Bup Med [a,b]	47.3 (no) 48.3 (yes) 4.3 (missing)	48.7 (no) 50.2 (yes) 1.1 (missing)	1.4 1.9 3.2	0.006	48.1 (no) 48.9 (yes) 3.0 (missing)	44.9 (no) 52.3 (yes) 2.8 (missing)	3.2 3.4 0.2	0.067

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Includes past ordered or dispensed buprenorphine medications

[c] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered and/or dispensed) with indicator for missing (18 missing)

3.13 Proportions of covariates and standardized differences for past year depression limited to patients with at least a year of observation prior to first OUD diagnosis with a) excluding past year mental illness diagnoses from IPTW; b) excluding past year mental illness and substance use disorder diagnoses from IPTW

a. Past year depression: excluding prior mental illness from propensity score model and IPTW

	Crude (Unweighted)				Weighted (stabilized)[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=104)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=328)	OUD w prior DEP (n=102)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	33.7	4.2	-0.088	36.2	32.7	3.5	-0.073
30-39	36.1	39.4	3.3	0.068	37.6	44.7	7.1	0.147
40-49	15.9	14.4	1.5	-0.041	15.5	11.4	4.1	-0.114
50+	10.1	12.5	2.4	0.075	10.7	11.1	0.4	0.015
Male sex	59.5	43.3	16.2	-0.329	54.7	48.2	6.5	-0.132
Non-Hispanic Ethnicity	98.8	97.1	1.7	-0.122	98.1	98.4	0.3	0.018
White race	99.4	100.0	0.6	0.108	100.0	100.0	0.0	0.000
Prior SU dx[a]	28.9	73.1	44.2	0.982	39.8	46.5	6.7	0.150
Prior Med dx[a]	12.1	40.4	28.3	0.675	19.2	21.9	2.7	0.065
Prior HIV/ Hep C dx[a]	1.4	5.8	4.4	0.233	2.8	3.0	0.2	0.014
Prior chronic pain dx[a]	6.1	21.2	15.1	0.449	9.7	11.1	1.4	0.042
Prior bup med [a,b]	46.5	39.2	7.3	-0.148	44.2	40.2	4.0	-0.082

b. Past year depression: excluding prior mental illness and substance use disorder from propensity score model and IPTW

	Crude (Unweighted)				Weighted (stabilized)[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=104)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=328)	OUD w prior DEP (n=102)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	33.7	4.2	-0.088	36.7	35.7	1.0	-0.019
30-39	36.1	39.4	3.3	0.068	36.6	37.2	0.6	0.012
40-49	15.9	14.4	1.5	-0.041	16.2	18.1	1.9	0.051
50+	10.1	12.5	2.4	0.075	10.5	9.0	1.5	-0.047
Male sex	59.5	43.3	16.2	-0.329	54.6	52.0	2.6	-0.053
Non-Hispanic Ethnicity	98.8	97.1	1.7	-0.122	97.4	98.2	0.8	0.057
White race	99.4	100.0	0.6	0.108	100.0	100.0	0.0	0.000
Prior Med dx[a]	12.1	40.4	28.3	0.675	19.0	19.2	0.2	0.007
Prior HIV/ Hep C dx[a]	1.4	5.8	4.4	0.233	2.8	3.0	0.2	0.011

Prior chronic pain dx[a]	6.1	21.2	15.1	0.449	10.0	10.1	0.1	0.004
Prior bup med [a,b]	46.5	39.2	7.3	-0.148	44.2	43.7	0.5	-0.010

c. Past year depression: with IPTW including missing indicator variable for buprenorphine medications

	Crude (Unweighted)				Weighted (stabilized) w missing[c]			
	OUD wo prior DEP (n=346)	OUD w prior DEP (n=104)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=343)	OUD w prior DEP (n=104)	Difference in proportions	Standardized differences
Age Category								
18-29	37.9	33.7	4.2	-0.088	35.3	39.8	4.5	0.093
30-39	36.1	39.4	3.3	0.068	39.2	38.6	0.6	-0.011
40-49	15.9	14.4	1.5	-0.041	14.9	9.2	5.7	-0.157
50+	10.1	12.5	2.4	0.075	10.6	12.4	1.8	0.054
Male sex	59.5	43.3	16.2	-0.329	54.8	39.6	15.2	-0.309
Non-Hispanic Ethnicity	98.8	97.1	1.7	-0.122	98.7	98.3	0.4	-0.027
White race	99.4	100.0	0.6	0.108	100.0	100.0	0.0	0.000
Prior year MH dx[a]	14.5	74.0	59.5	1.494	29.7	36.1	6.4	0.150
Prior year SU dx[a]	28.9	73.1	44.2	0.982	41.2	48.4	7.2	0.152
Prior year Med dx[a]	12.1	40.4	28.3	0.675	20.2	24.4	4.2	0.109
Prior year HIV or Hep C dx[a]	1.4	5.8	4.4	0.233	2.2	4.0	1.8	0.092
Prior year Chronic Pain dx[a]	6.1	21.2	15.1	0.449	9.0	10.6	1.6	0.054
Prior year Bup Med [a,b]	51.2 (no)	59.6 (no)	8.4	-0.195	53.8 (no)	61.8 (no)	8.0	-0.170
	44.5 (yes)	38.5(yes)	6.0		42.7 (yes)	36.2 (yes)	6.5	
	4.3 (missing)	1.9 (missing)	2.4		3.5 (missing)	2.0 (missing)	1.5	

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Includes past ordered or dispensed buprenorphine medications

[c] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered and/or dispensed) with indicator for missing (20 missing)

3.14 Proportions for each covariate and standardized differences before and after weighting for *all prior* diagnoses and *all observation time* prior to first OUD diagnosis date

	Crude (Unweighted)				Weighted (stabilized)[c]			
	OUD wo prior DEP (n=447)	OUD w prior DEP (n=274)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=423)	OUD w prior DEP (n=270)	Difference in proportions	Standardized differences
Age Category								
18-29	37.8	34.7	3.1	-0.065	37.5	41.4	3.6	0.080
30-39	36.9	36.4	0.5	-0.009	35.6	33.9	1.7	-0.038
40-49	15.4	15.3	0.1	-0.003	15.1	15.0	0.1	-0.001
50+	9.8	13.5	3.7	0.114	11.7	9.7	2.0	-0.061
Male sex	60.0	40.1	19.9	-0.404	51.0	49.8	1.2	-0.026
Non-Hispanic Ethnicity	97.1	98.2	1.1	0.071	97.4	97.2	0.2	-0.013
White race	98.7	99.6	0.9	0.106	99.0	99.6	0.6	0.065
Prior MH dx[a]	30.4	79.9	49.5	1.146	51.4	52.8	1.4	0.034
Prior SU dx[a]	53.2	88.3	35.1	0.835	68.2	70.9	2.7	0.065
Prior Med dx[a]	23.7	46.7	23.0	0.495	33.6	34.9	1.3	0.030
Prior HIV/ Hep C dx[a]	6.7	12.4	5.7	0.194	10.2	10.0	0.2	-0.007
Prior chronic pain dx[a]	14.5	28.5	14.0	0.343	21.8	23.8	2.0	0.051
Prior bup med [a,b]	49.5	50.2	0.7	0.013	49.6	51.0	1.4	0.027

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Includes past ordered or dispensed buprenorphine medications; Unweighted sample sizes: OUD without prior DEP n=424, OUD with prior DEP n=271; Weighted sample sizes: OUD without prior DEP n=423, OUD with prior DEP n=270

[c] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered and/or dispensed)

3.15 Proportions for each covariate and standardized differences before and after weighting *for past year* diagnoses and *all observation time* prior to first OUD diagnosis date

	Crude (Unweighted)				Weighted (stabilized)[d]			
	OUD wo past year DEP (n=457)	OUD w past year DEP (n=111)	Difference in proportions	Standardized differences	OUD wo past year DEP (n=417)	OUD w past year DEP (n=109)	Difference in proportions	Standardized differences
Age Category								
18-29	37.8	34.2	3.6	-0.074	36.9	44.5	7.6	0.159
30-39	36.9	38.7	1.8	0.038	38.1	34.3	3.8	-0.078
40-49	15.4	15.3	0.1	-.003	14.5	9.2	5.3	-0.148
50+	9.8	11.7	1.9	0.060	10.5	12.0	1.5	0.049
Male sex	60.0	44.1	15.9	-0.320	56.0	42.9	13.1	-0.266
Non-Hispanic Ethnicity	97.1	97.3	0.2	0.013	97.9	98.0	0.1	0.010
White race	98.7	100.0	1.3	0.165	100.0	100.0	0.0	0.000
Prior year MI dx[b]	13.2	72.1	58.9	1.477	27.1	32.7	5.6	0.142
Prior year SUD dx[b]	26.0	72.1	46.1	1.037	37.6	44.5	6.9	0.155
Prior year Med dx[b]	10.7	38.7	28.0	0.684	18.1	24.2	6.1	0.149
Prior year HIV/ Hep C dx[b]	1.3	5.4	4.1	0.226	1.6	2.7	1.1	0.058
Prior year chronic pain dx[b]	4.7	20.7	16.0	0.494	7.9	10.0	2.1	0.062
Prior year bup med[b,c]	46.5	38.5	8.0	-0.160	44.2	36.9	7.3	-0.148

[a] OUD without past year DEP= no depression OR depression on/after first OUD dx (n=447); OUD with past year DEP=had at least one depression code within year prior to first OUD dx (n=111); Patients that had a depression code more than a year prior to the first OUD dx and didn't have another are excluded (n=163)

[b] The definition of all of these DO NOT include the day of OUD dx (e.g. within 1 year prior to first OUD dx date)

[c] Includes past ordered or dispensed buprenorphine medications; Unweighted sample sizes: OUD without prior DEP n=424, OUD with prior DEP n=109; Weighted sample sizes: OUD without prior DEP n=417, OUD with prior DEP n=109

[d] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior year mental illness diagnosis code, prior year substance use disorder diagnosis code, prior year Medical diagnosis code, prior year HIV or Hep C diagnosis code, prior year chronic pain diagnosis code, prior year buprenorphine prescription (ordered and/or dispensed)

Chapter 4: The role of comorbid depression in the continuity of buprenorphine treatment for opioid use disorder

4.0 Abstract

Background: Ongoing opioid agonist treatment, including methadone and buprenorphine, is associated with positive treatment outcomes. However, challenges with continuation and retention in opioid agonist treatment exist. Psychiatric comorbidities are associated with lower retention in substance use treatment, but this is not always consistent with opioid agonist treatment. Opioid use disorder and depression are highly comorbid and depression could impact the continuation and retention in buprenorphine treatment. The current study assessed differences in buprenorphine treatment continuity and retention among persons with opioid use disorder with and without co-occurring depression.

Methods: Records for ordered prescriptions placed within the Geisinger Health System between 2018 and 2019 were analyzed for patients who had an opioid use disorder and initiated buprenorphine treatment at specialty outpatient substance use treatment clinic (N=517). Co-occurring depression was defined as having any prior or past year depression diagnoses. We used propensity score weighted logistic regression to estimate odds of 180-day retention and any treatment discontinuation, and propensity score weighted cox proportional hazards regression to estimate hazard of treatment gaps or discontinuation for those with and without depression.

Results: Forty percent of the study sample remained in treatment at 180 days without any treatment gaps or discontinuation. Any prior or past year depression was associated with increased risk of treatment gap and/or discontinuation of treatment (any prior: weighted HR 1.54, 95% CI 1.11, 2.14; past year: weighted HR 1.84, 95% CI 1.16, 2.94). Past year depression was associated with decreased odds of 180-day retention (weighted OR 0.31; 95% CI 0.12, 0.79).

Conclusions: The association between co-occurring depression and opioid agonist treatment course and outcomes is not clear-cut, and the results of the current study further demonstrate this complexity. The results suggests that assessing and managing depression may be important for continuous engagement and longer-term retention in buprenorphine treatment.

4.1 Introduction

Over two million adults in the US met the criteria for an opioid use disorder in 2018.[11] Opioid use disorder is associated with increased risk of mortality, as well as other health conditions and social adversity.[109] However, effective treatment for opioid use disorder exists and its expansion is crucial for reducing morbidity and mortality associated with opioid use disorder. The use of opioid agonist medications, including methadone and buprenorphine, is the gold standard for the treatment of opioid use disorder (OUD).[32] Buprenorphine which is most typically prescribed through office-based or outpatient treatment is the focus of this study. Buprenorphine is a partial opioid agonist and has been found to be effective in the treatment of OUD in clinical trials,[37,44] as well as a number of observational studies. Buprenorphine is effective in reducing opioid withdrawal symptoms and decreasing use of opioids.[44,110] Compared to non-medication based treatment, buprenorphine is associated with reductions in other adverse effects of OUD including criminal justice involvement, HIV and Hepatitis C transmission and overdose death.[27,37–41] Buprenorphine is also associated with greater treatment retention[37] and ongoing maintenance is particularly crucial in treating OUD and reducing adverse consequences.[60,111,112]

Even with the strong evidence base for the use of agonist medications to treat OUD, significant barriers to accessing and utilizing medication for opioid use disorder (MOUD) exist, leading to less than 30% of people with OUD receiving medication as part of their treatment plan.[113] In the US, healthcare providers must have an approved waiver to prescribe buprenorphine. Even though the prevalence of buprenorphine-waivered providers increased from 3.8 per 100,000 persons in 2007 to 17.3 per 100,000 persons in 2017, this corresponds to fewer than 10% of providers in the US.[36] The expansion of waivered providers was also not uniform

across communities. The growth of buprenorphine waivered providers was slower in non-metropolitan counties compared to metropolitan counties. Furthermore, counties with lower levels of education overall also had slower growth compared to those with higher education levels.[36] Even though the percentage of outpatient substance use treatment facilities that offer buprenorphine has increased in recent years, as of 2016 only 25% of these facilities offered buprenorphine.[35]

Even among individuals with OUD who do receive treatment with MOUD, challenges with low adherence and treatment retention exist.[114] Ongoing maintenance treatment with buprenorphine is associated with better outcomes. Current clinical guidelines recommend a minimum of 180 days of treatment with MOUD, but continued treatment without a specific duration is advised.[115,116] A number of studies have explored risk factors for MOUD continuity and discontinuity. At the patient-level, male sex, younger age, and non-white race and Hispanic ethnicity status are associated with earlier discontinuation of buprenorphine treatment.[48,117] Other substance use and medical comorbidities including chronic pain and Hepatitis C were also found to be associated with greater risk of discontinuation.[48]

The role of psychiatric comorbidities in the course of opioid agonist treatment for OUD is unclear. While it is well established that psychiatric comorbidity is associated with reduced access and lower retention to substance use treatment overall,[22,23] evidence is less clear for opioid agonist treatment. Krawcyzk and colleagues used a national dataset of substance use treatment programs in the US and found no association between psychiatric comorbidity and opioid agonist treatment non-completion and a weak association with time to attrition from agonist treatment.[22] In another study utilizing Medicaid claims, Samples and colleagues also did not find an association between psychiatric comorbidities, including depression, anxiety, post-

traumatic stress disorder, bipolar disorder and schizophrenia, and minimum treatment duration or time to buprenorphine treatment discontinuation.[48]

Among persons with OUD, depression is the most common psychiatric comorbidity.[16] Research examining the relationship between depression and opioid agonist treatment course is mixed with some studies finding no effect[48] and others finding depression associated with positive treatment outcomes.[53] A limitation of existing studies is relatively short duration of treatment follow-up of 12 weeks.[53,54]

Given the prevalence of depression among persons with OUD, more research examining the relationship between co-occurring depression and course of buprenorphine treatment is needed. Longer follow-up is particularly necessary, as ongoing buprenorphine treatment leads to better outcomes. The current study aimed to explore the association between depression with gaps, discontinuation and retention in buprenorphine treatment for OUD. We utilized data on ordered prescriptions over time for patients who initiated buprenorphine treatment at a specialty treatment facility within an integrated healthcare system in Pennsylvania.

4.2 Methods

Study setting and sample

Data on prescription medications ordered by prescribers for patients in the Geisinger Health System was used to assess buprenorphine treatment course. Patients included in the sample were recruited from one of four outpatient substance use treatment clinics within the Geisinger Health System starting in the spring of 2017. The primary treatment model in these clinics utilizes buprenorphine or naltrexone to treat OUD. These clinics also provide other services including counseling and care coordination to address other social factors impacting clinic patients. Treatment information is embedded into the electronic health records of the

Geisinger Health system with the consent of patients receiving care. Specific details of the model used at these addiction medicine clinics are provided elsewhere.[74]

For patients recruited from one of these outpatient treatment clinics, all electronic health records and prescription medication orders up until fall 2019 were used. Across all patients in the study, there was an average of 248 days of follow-up after the start of treatment. In order for a patient to be included in the study sample, they must have met the following criteria: 1) at least one OUD diagnosis code; 2) at least 18 years old at the date of first OUD code; 3) at least one ordered buprenorphine prescription; 4) at least one visit at one of the four Geisinger outpatient treatment clinics; and 5) at least one year of electronic health records data prior to the date of first OUD diagnosis. The prescription records also included a limited number of buprenorphine prescriptions in inpatient settings. These prescription records were excluded. The final analytic sample included 517 adults and 9,729 buprenorphine prescriptions. The current study does not qualify as human subjects research as determined by Geisinger and Johns Hopkins Bloomberg School of Public Health Intuitional Review Boards.

Independent measures

Primary exposure and covariates. All patients in the study sample had at least one OUD diagnosis code in their electronic health records. The primary exposure variable of interest was a depression diagnosis code prior to the date of first OUD diagnosis. Because the association of buprenorphine treatment continuity with depression may vary according to the recency of depression, analyses were conducted once for all depressive disorders diagnosed before the first OUD diagnosis in the system and separately for depression diagnoses within 12 months prior to first OUD diagnosis. Other covariates included sex, age at OUD diagnosis date, race, ethnicity, mental illness (MI) other than depression, substance use disorder (SUD) other than OUD, HIV or

Hepatitis C diagnosis, chronic pain diagnosis, and other common medical diagnoses (hypertension, diabetes mellitus, and disorders of the airway including chronic obstructive pulmonary disease [COPD] and asthma), all prior to date of first OUD diagnosis. All medical and mental health and substance use diagnoses were defined using ICD 9 or 10 codes listed in Supplemental Table 4.1.

Buprenorphine products. All oral and extended-release injectable buprenorphine formulations were included (Table of all medications is included in Supplemental Table 4.2).

Outcome measures

1. Treatment gap was defined by an absence of buprenorphine prescriptions for at least 14 days but less than 30 days for non-extended release formulations,[117] and at least 44 days but less than 60 days for extended release formulations.

2. Treatment discontinuation was defined by an absence of buprenorphine prescriptions of 30 days or longer for non-extended release formulations[48] and 60 or longer for extended release formulations. For extended release formulations, the definition was based on a typical once-monthly injection.

3. Total treatment length was quantified as the total number of days between first outpatient substance use clinic visit date with a buprenorphine prescription and date of last buprenorphine prescription in ordered prescription records.

4. Treatment retention was a binary measure of treatment of at least 180 days without treatment gaps or discontinuation following first clinic visit.[48,117]

5. Treatment continuity was a time-to-event measure assessed by the total number of days between first buprenorphine prescription and the first day of discontinuation or gap.

Analyses

The goal of this study was to compare medication continuity and discontinuity between individuals with and without depression. To do this we used propensity score weighted regression models. The propensity score methods were used to account for potential confounding variables and to create groups with and without prior depression with a balanced distribution of observed covariates, stabilized inverse probability of treatment weights (IPTW) were calculated from propensity scores derived using logistic regression. Separate weights were computed for the two exposures of interest: OUD with any prior depression and OUD with past year depression. For any prior depression, propensity scores were constructed using patient characteristics and relevant diagnoses that occurred at any point prior to first OUD diagnosis, including other mental health disorders, other substance use disorders, medical conditions, HIV or Hepatitis C, and chronic pain, as well as any ordered buprenorphine prescriptions. For past year depression, patient characteristics and diagnostic codes that occurred within the year prior to first OUD diagnosis were used to construct propensity scores. After applying IPTW, we observed substantial reductions in differences in the distribution of covariates between the OUD without prior depression and OUD with prior depression and past year depression groups. Crude and standardized differences in covariate proportions are presented in Supplemental Tables 4.3 and 4.4. Absolute standardized mean differences are used to assess covariate balance with propensity score methods. In prior research, thresholds of 0.1 and 0.25 have been used to identify imbalance.[100] For all prior depression, after applying weights, standardized differences for all covariates were less than 0.1. After applying weights for past year depression, the absolute standardized difference was greater than 0.1 for age categories 18-29 and 40-49, past year mental illness diagnoses and past year substance use disorder diagnoses. The standardized difference for sex was greater than 0.25 (Supplemental Table 4.4). To account for potential imbalance after

applying weights, we also included these imbalanced variables in the weighted regression models for past year depression.

Weighted regression models were used to then examine the association between 1) any depression; and 2) past year depression with each of the outcomes. For binary outcomes (180-day retention and treatment discontinuation), logistic regression was used to obtain unweighted and propensity score weighted odds ratios. Weighted regression models also included time since OUD diagnosis, time since first buprenorphine prescription (if occurred prior to first clinic visit), and time between first clinic visit and last buprenorphine prescription record.

For days to gap or discontinuation, and days to treatment discontinuation, we used Cox proportional hazards model to calculate unweighted and propensity-score weighted proportional hazards ratios. The time origin was first clinic date with a buprenorphine prescription. In addition to IPTW, in these analyses we also adjusted for time since OUD diagnosis and time since first buprenorphine prescription (if they occurred prior to first clinic visit). Robust standard errors were applied to account for correlated observations (multiple prescriptions) per patient.[102] Weighted Kaplan-Meier survival curves for treatment gaps or discontinuation and treatment discontinuation based on depression exposure were also plotted. All analyses were conducted using Stata 14.2.

Sensitivity analyses

Because of prescribing and procedural differences between extended-release and non-extended-release buprenorphine products, we repeated all analyses after excluding patients who had any extended-release buprenorphine prescriptions (n=37). We also re-ran models excluding patients whose first buprenorphine prescription order was after their first medication clinic visit date (n=30).

4.3 Results

Sample characteristics

Unweighted descriptive information of patient demographic characteristics and diagnoses is presented in Table 4.1. Relative to patients with OUD without co-occurring depression, a larger proportion of patients with OUD and co-occurring depression (both any depression diagnoses captured prior to OUD diagnosis for a given patient and depression diagnoses in the year prior to OUD diagnosis) were female and had other co-occurring health conditions. Without accounting for gaps, the average number of days between the first clinic date and last buprenorphine prescription was 248 days for patients without a prior depression diagnosis, 282 days for those with any prior depression diagnosis and 344 days for those with a past year depression diagnosis (Table 4.2).

Thirty-three percent of patients with OUD without depression had at least one treatment gap or discontinuation, whereas 41.9% with prior depression (p=0.03) and 50% with past year depression (p=0.004) had at least one gap or discontinuation. Overall, 16.7% of patients without depression, 20.7% of those with any prior depression (p=0.24) and 28.1% with past year depression (p=0.02) discontinued treatment at least once. The proportion of patients on buprenorphine for at least 180 days without gaps or discontinuation were 38.3% for OUD without depression, 41.0% for OUD with any prior depression (p=0.54) and 46.3% for OUD with past year depression (p=0.19) (Table 4.2).

Differences in any discontinuation and 6-month retention by depression exposure group

After applying IPTW, compared to patients with OUD but no prior depression, patients with OUD and past year depression had decreased odds of 6-month retention (weighted odds ratio (OR) 0.31; 95% CI 0.12, 0.79) and increased odds of any treatment discontinuation

(weighted OR 2.50; 95% CI 1.08, 5.75). There were no significant differences in odds of 6-month retention or odds of any treatment discontinuation between individuals with OUD without prior depression and individuals with OUD with any prior depression (Table 4.3).

Risk of gap or discontinuation by depression exposure group

Hazard ratios comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression and those with OUD and any prior or past year depression are presented in Table 4.4. Compared to patients without prior depression, patients with any prior depression or past year depression had an increased hazard of a treatment gap or discontinuation (any prior depression: weighted HR 1.54, 95% CI 1.11, 2.14; past year depression: weighted HR 1.84, 95% CI 1.16, 2.94) and treatment discontinuation (any prior depression: weighted HR 1.63, 95% CI 1.01, 2.63; past year depression: weighted HR 2.04, 95% CI 1.08, 3.87). Figure 4.1 displays weighted survival curves for each outcome.

Sensitivity analyses

After excluding patients who had any extended release buprenorphine prescriptions, past year depression was no longer associated with odds of 6-month retention or any discontinuation, although the direction and magnitude of the odds ratios did not change meaningfully (6-month retention: weighted OR 0.60, 95% CI 0.20, 1.83; any discontinuation: weighted OR 1.45, 95% CI 0.43, 4.86). Past year depression was also no longer significantly associated with increased hazard of gap or discontinuation, but was still associated with increased rate of discontinuation. However, as with the binary outcomes the direction and strength of the effect was similar (weighted HR 1.64, 95% CI 0.92, 2.94). After excluding patients who had a first buprenorphine prescription order after their first medication clinic visit date, past year depression was no longer significantly associated with decreased odds of 6-month retention (weighted OR 0.41, 95% CI

0.16, 10.5) or odds of any discontinuation (weighted OR 2.34, 95% CI 0.96, 5.71). Also, any prior and past year depression were no longer significantly associated with increased hazard of discontinuation (all prior weighted HR 1.64, 95% CI 0.99, 2.70; past year weighted HR 1.85, 95% CI 0.96,3.54). The direction and magnitude of the effects were similar to the main analyses.

4.4 Discussion

The current study examined differences in continuity of and retention in buprenorphine treatment for OUD among persons with and without a prior depression diagnosis. Similar to prior studies,[48,117] we found that only 39.5% of the overall patient sample remained in treatment at 6-months without any treatment gaps or discontinuation. As compared to those without a prior depression diagnosis, persons who had any prior or past year depression diagnoses had increased risk of a treatment gap and/or discontinuation of treatment. Persons with past year depression were less likely to still be in buprenorphine treatment at 180 days.

Across substance use treatment outcomes, psychiatric comorbidities including depression have been found to be associated with reduced access and lower retention.[22,23] However, this association between course and outcomes of opioid agonist treatment, including both buprenorphine and methadone, and psychiatric comorbidity,[22,50,118] and specifically depression,[48,53,119,120] is not as straightforward. The results of our study further add to the complexity of this relationship. We found persons with OUD and any prior or past year depression had greater risk of a gap in their buprenorphine prescriptions, as well as a greater risk of discontinuing treatment. We also found that patients with a depression diagnosis in the year prior to their first OUD diagnosis were less likely to still be receiving buprenorphine prescriptions at 180 days. This could be impacted by a number of factors. It may be that symptoms of depression impact a person's ability to adhere to treatment regimen and

requirements of the clinic where they are receiving treatment, and thus also influence treatment continuity and discontinuation. Prior studies have also found that persons with co-occurring mental health disorders, including depression, may have more complex treatment needs. Many have other medical comorbidities and social factors that are not always incorporated into substance use treatment programs, including medication based treatment for OUD.[86,121,122] This is also true for our study population, in which the majority for persons with a prior depression diagnosis also had another mental health or substance use disorder. Almost 50% had a prior medical diagnosis, including hypertension, diabetes mellitus, COPD and/or asthma, and 31% had a prior chronic pain diagnosis. However, we utilized propensity score methods to create groups with and without depression with similar covariate balance with the goal of separating the effect of depression from the effects of pre-existing differences in observed covariates. Therefore, the results suggest that depression may be playing a key role in continuity and retention in treatment.

We were unable to assess changes in depressive symptoms among the study population. However, prior research suggests that buprenorphine is associated with improvement in depressive symptoms.[123] This could be because of antidepressant properties of buprenorphine. A partial opioid agonist, buprenorphine is a mu receptor agonist and kappa receptor antagonist. The kappa receptor system is involved in the expression of depressive symptoms and kappa agonists increase depressive symptoms including dysphoria. Thus, kappa antagonist properties of buprenorphine may counteract these effects and improve depressive symptoms among patients.[124,125] It is important to extend this understanding by exploring changes in depression with longer term buprenorphine treatment and further assess how these changes in depressive symptoms might influence course of treatment and outcomes.

In this study we did not examine the possible moderating effect of depression treatments, and specifically antidepressant medications, in the association of depression with buprenorphine treatment continuity. However, past research has found scant evidence for any beneficial effects of antidepressant treatments on opioid agonist treatment outcomes or reduction in depressive symptoms among persons with co-occurring OUD and depression.[57,123] Although, the addition of psychotherapies may be helpful in reducing symptoms of distress among this population.[123] More research is needed on the potential benefit of psychotherapies on buprenorphine treatment outcomes among persons with co-occurring OUD and depression. Lastly, it would be interesting to explore potential differences in support group participation, as well as the role of instrumental support in treatment retention particularly for individuals with co-occurring depression.

Limitations

As with other studies assessing this complex relationship between opioid agonist treatment and depression, there are a number of limitations related to measurement that need to be considered. First, we relied on diagnostic codes from electronic health records to define OUD, depression and other health conditions which rely on the consistency and accuracy of the recordings by healthcare providers. However, because this population was recruited from an outpatient substance use treatment clinic, addiction specialists verified the OUD diagnosis. Also, differences in observation time prior to first OUD diagnosis could impact likelihood of receiving diagnoses because of differences in contact with the health system. While some of this variation could be accounted for by including age in the propensity score model, as well as limiting to past year diagnoses, future plans include accounting for this. We also note that each time we use "first date," it is referring to the first date in the electronic health records or prescription medication database, which may or may not be a person's first ever diagnosis or prescription. Relying on

ordered buprenorphine prescriptions to measure continuity and retention in treatment may also create some limitations because receiving a prescriptions is not necessarily an indicator of taking a medication. To mitigate this, we chose to only include patients who initiated treatment at one of the Geisinger clinics, which have detailed protocols to track treatment compliance. Additionally, after excluding patients based on having extended release buprenorphine prescriptions and those whose first buprenorphine prescription was after their first clinic date, we lost statistical significance for some of the results. This could be because of the reduction in sample size, however future research should examine this more closely, particularly for treatment including extended release buprenorphine formulations. Also, clinic differences, such as location and providers, could influence treatment course and outcomes; we plan to request this information and then account for it in future analyses. Lastly, the study sample includes almost exclusively white non-Hispanic patients receiving healthcare in rural Pennsylvania. Therefore, the results may not generalize to more racially diverse and urban populations.

Conclusions

The results of the current study suggest that prior depression is relatively common among patients with OUD and, often associated with other comorbidities. Furthermore, depression is associated with reduced continuity and retention in buprenorphine treatment. These findings highlight the need for improved depression care, ideally in the context of integrated services, for this large and vulnerable group of patients with OUD.

Table 4.1 Unweighted sample characteristics and prior diagnoses in the electronic health records (N=517)

	OUD without prior depression (n=300)	OUD with any prior depression (n=217)	OUD with any past year depression (n=82)
Demographic characteristics	%	%	%
Male sex	57.3	38.7	42.7
Age group[a]			
18-29	37.0	32.7	34.2
30-39	36.3	36.3	39.0
40-49	16.3	16.1	15.9
50+	10.3	11.8	11.0
Non-Hispanic ethnicity	99.0	97.7	96.3
White race	99.3	99.5	100.0
Any prior diagnoses or prescription			
Mental illness	37.0	79.7	--
Substance use disorder	64.7	88.0	--
Chronic pain	20.3	30.9	--
HIV or Hepatitis C	9.0	11.5	--
Other medical condition[a]	31.0	47.9	--
Buprenorphine prescription[b]	3.7	11.1	--
Past year diagnoses or prescription			
Mental illness	15.0	--	73.2
Substance use disorder	27.3	--	69.5
Chronic pain	6.7	--	23.2
HIV or Hepatitis C	1.7	--	4.9
Other medical condition[a]	13.0	--	39.0
Buprenorphine prescription[b]	1.0	--	3.7

[a] Other medical conditions include hypertension, diabetes mellitus, and chronic obstructive pulmonary disease and asthma

[b] Ordered

Table 4.2 Description of first dates of opioid use disorder, buprenorphine order and medication clinic, and frequency of treatment outcomes by exposure group

	Total sample (n=517)		OUD without prior depression (n=300)		OUD with any prior depression (n=217)		OUD with any past year depression (n=82)	
First dates	Median [range]		Median [range]		Median [range]		Median [range]	
First OUD dx date	8/23/2018 [7/16/1998, 7/16/2019]		9/14/2018 [7/16/1998, 7/16/2019]		6/18/2018 [7/26/2005, 7/15/2019]		10/19/2018 7/26/2005, 7/15/2019]	
First buprenorphine order	11/6/2018 [10/16/2003, 7/16/2019]		12/11/2018 [1/21/2017, 7/16/2019		9/22/2018 [10/16/2003, 7/15/2019]		8/2/2018 [10/22/2003, 7/15/2019]	
First medication clinic visit	11/28/2018 [4/14/2017, 7/16/2019]		12/14/2018 [4/14/2017, 7/16/2019]		10/22/2018 [5/14/2017, 7/15/2019]		8/24/2018 [10/27/2017, 7/15/2019]	
Buprenorphine treatment outcomes	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Total length (without gaps)[a]	262.1 (196.0)		247.6 (186.5)		282.1 (207.2)		343.6 (219.9)**	
	n (%)	Mean # (SD)	n (%)	Mean # (SD)	n (%)	Mean # (SD)	n (%)	Mean # (SD)
Any gap[b]	118 (22.8)	0.27 (0.56)	58 (19.3)	0.23 (0.51)	60 (27.7)*	0.34 (0.61)	26 (31.7)*	0.40 (0.66)
Number of gaps								
0	399 (77.2)		242 (80.7)		157 (72.4)		56 (68.3)	
1	99 (19.2)		49 (16.3)		50 (23.0)		20 (24.4)	
2 or more	19 (3.6)		9 (3.0)		10 (4.6)		6 (7.3)	
Any discontinuation[b]	95 (18.4)	0.22 (0.51)	50 (16.7)	0.20 (0.50)	45 (20.7)	0.24 (0.52)	23 (28.1)*	0.37 (0.66)
Number of discontinuations								
0	422 (81.6)		250 (83.3)		172 (79.3)		59 (72.0)	
1	82 (15.9)		44 (14.7)		38 (17.5)		17 (20.7)	
2 or more	13 (2.5)		6 (2.0)		7 (3.2)		6 (7.3)	
Any gap or discontinuation[b]	189 (36.6)	0.49 (0.77)	98 (32.7)	0.43 (0.72)	91 (41.9)*	0.58 (0.84)	41 (50.0)*	0.77 (0.99)
Number of gaps or discontinuations								
0	328 (63.4)		202 (67.3)		126 (58.1)		41 (50.0)	
1	142 (27.5)		76 (25.3)		66 (30.4)		26 (31.7)	
2 or more	47 (9.1)		22 (7.3)		25 (11.5)		15 (18.3)	
	n (%)		n (%)		n (%)		n (%)	
180-day retention[c]	204 (39.5)		115 (38.3)		89 (41.0)		38 (46.3)	

* p<0.05; reference group OUD without depression

** p<0.01; reference group OUD without depression

[a] Total length of time between first and last clinic date (in days)

[b] At least one

[c] Continuous (without gaps or discontinuation)

Table 4.3 Buprenorphine retention and discontinuation comparing adults with OUD without prior depression and those with OUD any prior/past year depression (Any prior depression: N=517, Past year depression: N=382)

	180 day retention[a]		Any discontinuation[b]	
	OR [95% CI]	Weighted OR [95% CI][c-e]	OR [95% CI]	Weighted OR [95% CI][c-e]
Any prior depression	1.12 [0.78, 1.60]	0.57 [0.33, 0.99]	1.31 [0.84, 2.05]	1.71 [0.97, 3.00]
Past year depression	1.39 [0.85, 2.27]	**0.31 [0.12, 0.79][f]**	**1.95 [1.10, 3.44]**	**2.50 [1.08, 5.75][f]**

[a] Continuous (without gaps or discontinuation)

[b] Defined as 30 or more days between buprenorphine prescriptions (60 days for extended release formulations)

[c] Stabilized IPTW for all prior depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx

[d] Regression model adjusted for time since first OUD diagnosis, time since first buprenorphine prescription (if occurred prior) and time between first and last medication-based clinic visit

[e] Stabilized IPTW for past year depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx

[f] Doubly robust model including sex, age categories 19-29 and 40-49, past year mental health disorder and past year substance use disorder in propensity score weight and adjusted regression model

Table 4.4 Hazard ratios with 95% confidence intervals (CI) for comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression (reference) and OUD with any prior/past year depression

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][e-h]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][e-h]
All prior depression[a,b]	189	1.95	1.25 [0.94, 1.66]	**1.54 [1.11, 2.14]**	95	0.85	1.22 [0.81, 1.82]	**1.63 [1.01, 2.63]**
Past year depression[c,d]	139	1.90	1.37 [0.95, 2.00]	**1.84 [1.16, 2.94]**	73	0.87	1.60 [0.97 2.65]	**2.04 [1.08, 3.87]**

[a] Crude N=517

[b] IPTW N=512

[c] Crude N=382

[d] IPTW N=370

[e] Stabilized IPTW for all prior depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

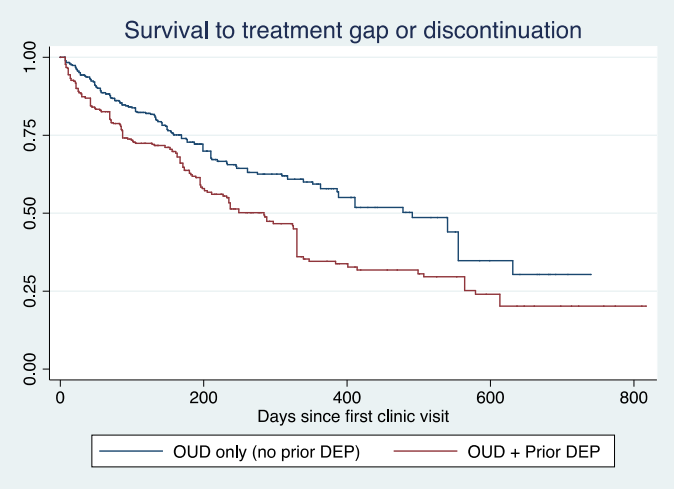
[f] Stabilized IPTW for past year depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

[g] For all prior depression, regression model adjusted for time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

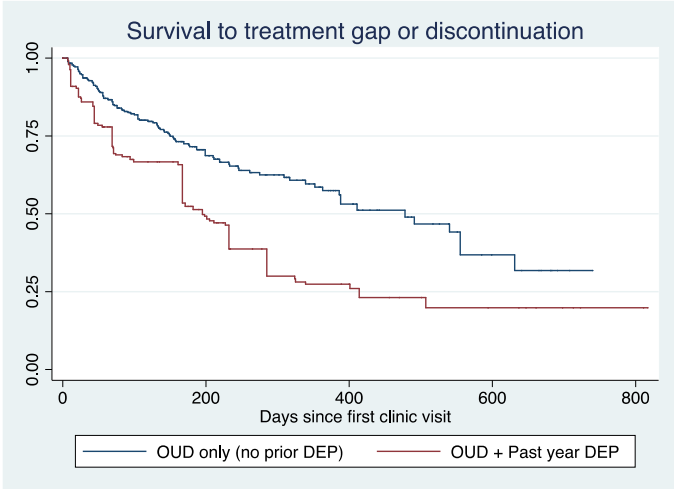
[h] For past year depression, regression model adjusted for sex, age categories 19-29 and 40-49, past year mental health disorder and past year substance use disorder, time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

Figure 4.1 Kaplan Meier survival curves for A) Gaps or discontinuations in buprenorphine treatment according to any prior depression diagnoses; B) Gaps or discontinuations in buprenorphine treatment according to past year depression diagnosis; C) Discontinuation in buprenorphine treatment according to any prior depression diagnoses; and D) Discontinuation in buprenorphine treatment according to past year depression diagnoses. All analyses weighted by Inverse Probability of Treatment Weights.

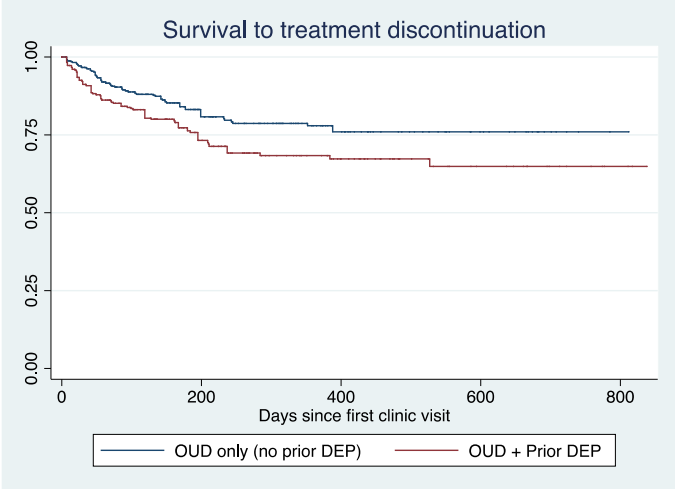
A.



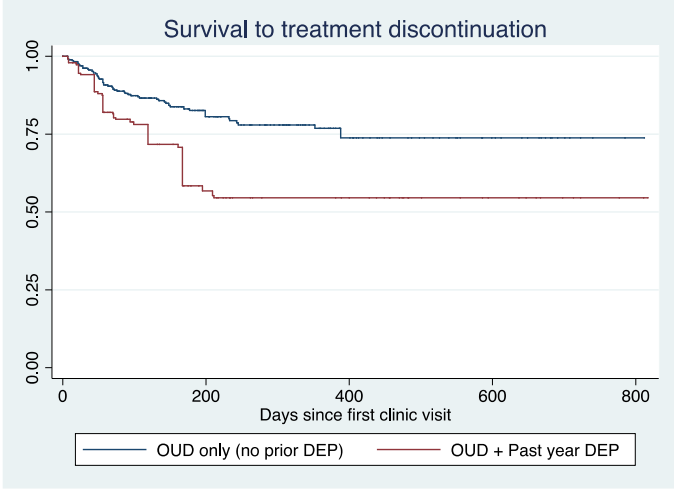
B.



C.



D.



Supplemental Table 4.1 ICD 9 and ICD 10 codes used to define diagnoses

Diagnosis categories	**Diagnosis Included**
Mental health and Substance use	
Opioid use disorder	ICD9: 304, 304.0, 304.00-.02, 305.5, 305.50-.52 ICD10: F11, F11.1, F11.10, F11.12, F11.120-.122, F11.129, F11.14, F11.15, F11.150-.151, F11.159, F11.18, F11.181-.182, F11.188, F11.19, F11.2, F11.20, F11.22, F11.220-.222", F11.229, F11.23-.25, F11.250-.251, F11.259, F11.28, F11.281-.282, F11.288, F11.29, F11.9, F11.90, F11.92, F11.920-.922, F11.929, F11.93-.95, F11.950-.951, F11.959, F11.98, F11.981-.982, F11.988, F11.99
Depressive disorders	ICD9: 296.2*, 296.3*, 300.4*, 311 ICD10: F32*, F33*, F34.1
Other substance use disorder	ICD9: 303*, 304.1*, 304.2*, 304.3*, 304.4*, 304.5*, 304.6*, 304.8*, 304.9*, 305.0*, 305.1*,305.2*, 305.3*, 305.4*, 305.6*, 305.7*, 305.9* ICD10: F10*, F12*-F19*, F55*
Other mental health disorder	ICD9: 290*-296*, 297*-299*, 300*, 301*, 302*, 308*, 309* ICD10: F01*-F09*, F20*-F25*, F28*-F29*, F31*, F34*, F39, F40*, F41.0, F41.1, F41.3, F41.8, F41.9, F42*-F45*, F48*, F50*-F52*, F54*, F59*, F60*, F63*-F69*, F99*
Other medical	
Chronic pain	ICD9: 338.2*, 338.4, ICD10: G89.2*, G89.4
HIV and Hepatitis C	ICD9: 042, 070.41, 070.44, 070.51, 070.54, 070.71 ICD10: B20, B17.1*, B18.2, B19.2*
Other *(includes hypertensive disease, diabetes mellitus, disorders of the airway-COPD and asthma)*	ICD9: 401*-405*, 205*, 490*-496* ICD10: I10*-I13*, I15*-I16*, E08*-E11*, E13*, J40*-J45*, J47*

Supplemental Table 4.2 List of Buprenorphine products, formulations and routes

Ordered Buprenorphine Medications	
Buprenorphine products	**Total overall=9,729 prescriptions (n, %)** Buprenorphine HCL (437, 4.5%) Buprenorphine HCL-Naloxone HCL (9,114, 93.7%) Buprenorphine ER (53, 0.5%) Sublocade (2, 0.02%) Suboxone, film and sublingual (112, 1.15%) Zubsolv, sublingual (11, 0.11%)
Buprenorphine formulations	Film (5,011, 51.5%) SL Tab (4,663, 47.9%) Solution prefilled syringe (55, 0.6%)
Buprenorphine routes	Subcutaneous (55, 0.6%) Sublingual (9,674 99.4%)

Supplemental Table 4.3 Proportions for each covariate and standardized differences comparing opioid use disorder without any prior depression and opioid use disorder with any prior depression before and after weighting for all prior diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis

	Crude (Unweighted)				Weighted (stabilized)[b]			
	OUD wo prior DEP (n=300)	OUD w prior DEP (n=217)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=300)	OUD w prior DEP (n=216)	Difference in proportions	Standardized differences
Age Category								
18-29	37.0	32.7	4.3	-0.090	35.4	37.6	2.2	0.047
30-39	36.3	36.3	0.0	0.021	37.2	35.5	1.7	-0.035
40-49	16.3	16.1	0.2	-0.006	15.8	16.0	0.2	0.107
50+	10.3	11.8	0.5	0.107	11.6	10.9	0.7	-0.023
Male sex	57.3	38.7	18.6	-0.379	48.4	48.4	0.0	-0.021
Non-Hispanic Ethnicity	99.0	97.7	1.3	-0.103	97.7	97.8	0.1	0.007
White race	99.3	99.5	0.2	0.027	99.5	99.6	0.1	0.015
Prior MH dx	37.0	79.7	42.7	0.960	55.5	57.6	2.1	0.048
Prior SU dx[a]	64.7	88.0	23.3	0.570	75.5	77.3	1.8	0.044
Prior Med dx[a]	31.0	47.9	16.9	0.351	37.4	38.9	1.5	0.032
Prior HIV/ Hep C dx[a]	9.0	11.5	2.5	0.083	11.2	11.2	0.0	-0.000
Prior chronic pain dx[a]	20.3	30.9	10.6	0.243	25.2	26.1	0.9	0.022
Prior buprenorphine rx[a]	3.7	11.1	7.4	0.285	7.2	7.5	0.3	0.014

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

Supplemental Table 4.4 Proportions for each covariate and standardized differences comparing opioid use disorder without past year depression and opioid use disorder with past year depression before and after weighting for all past year diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis

	Crude (Unweighted)				Weighted (stabilized)[b]			
	OUD wo past year DEP (n=300)	OUD w past year DEP (n=82)	Difference in proportions	Standardized differences	OUD wo past year DEP (n=298)	OUD w past year DEP (n=82)	Difference in proportions	Standardized differences
Age Category								
18-29	37.0	34.2	2.8	-0.059	34.8	39.8	4.8	0.105
30-39	36.3	39.0	2.7	0.055	38.9	39.2	0.6	0.005
40-49	16.3	15.9	0.4	-0.013	15.4	8.9	6.6	-0.176
50+	10.3	11.0	0.7	0.021	10.9	12.1	1.2	0.040
Male sex	57.3	42.7	14.6	-0.295	54.0	36.8	16.8	-0.347
Non-Hispanic Ethnicity	99.0	96.3	2.7	-0.176	98.5	98.0	0.5	-0.035
White race	99.3	100.0	0.7	0.116	100.0	100.0	0.0	0.000
Prior year MH dx[a]	15.0	73.2	58.2	1.439	28.2	34.5	6.1	0.156
Prior year SU dx[a]	27.3	69.5	42.2	0.927	37.9	42.8	5.2	0.108
Prior year Med dx[a]	13.0	39.0	26.0	0.618	19.5	23.1	4.0	0.086
Prior year HIV/ Hep C dx[a]	1.7	4.9	3.2	0.180	2.2	3.7	1.4	0.083
Prior year chronic pain dx[a]	6.7	23.2	16.5	0.474	9.8	10.8	1.0	0.031
Prior year buprenorphine rx[a]	1.0	3.7	2.7	0.176	1.8	2.5	0.7	0.044

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. within 1 year prior to first OUD dx date)

[b] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior year MI dx, prior year SUD dx, prior year Medical dx, prior year HIV or Hep C dx, prior year chronic pain dx, prior year buprenorphine prescription (ordered)

Chapter 4 Appendices

4.1 Timing between 1) First opioid use disorder diagnosis in EHR and first buprenorphine ordered prescription; 2) First opioid use disorder diagnosis in EHR and first medication-based treatment clinic; 3)) First buprenorphine ordered prescription and first medication-based treatment clinic

	Total sample (n=517)		**OUD without prior depression (n=300)**		**OUD with any prior depression (n=217)**		**OUD with any past year depression (n=82)**	
OUD dx timing (first Bup order)	n (%)	Median days [range]	n (%)	Median days [range]	n (%)	Median days [range]	n (%)	Median days [range]
First OUD dx before first bup order	186 (36.0)	586.5 [1, 7499]	108 (36.0)	665.5 [3, 7499]	78 (35.9)	494 [1, 4899]	38 (46.4)	568.5 [1, 4899]
First OUD dx on same day as first bup order	308 (59.8)		187 (62.3)		121 (55.8)		41 (50.0)	
First OUD dx after first bup order	23 (4.5)	3127 [7, 5392]	5 (1.7)	392 [185, 4511]	18 (8.3)	3718 [7, 5392]	3 (3.6)	2600 [19, 4117]
OUD dx timing (first MAT)	n (%)	Median days [range]	n (%)	Median days [range]	n (%)	Median days [range]	n (%)	Median days [range]
First OUD dx before first MAT visit	189 (36.6)	764 [1, 7499]	105 (35.0)	921 [6, 7499]	84 (38.7)	618.5 [1, 4899]	40 (48.8)	897 [1, 4899]
First OUD dx on same day as first MAT visit	328 (63.4)		195 (65.0)		133 (61.3)		42 (51.2)	
First Bup and MAT timing	n (%)	Median [range]	n (%)	Median [range]	n (%)	Median [range]	n (%)	Median [range]
First Bup order before first MAT visit	49 (9.5)	1046 [1, 5393]	19 (6.3)	217 [1, 4511]	30 (13.8)	2870.5 [4, 5393]	9 (10.9)	477 [15, 5377]
First Bup order on same day as first MAT visit	438 (84.7)		265 (88.3)		173 (79.7)		67 (81.7)	
First Bup order after first MAT visit	30 (5.8)	10.5 [1,404]	16 (5.3)	18 [3, 336]	14 (6.5)	9.5 [1, 404]	6 (7.3)	7 [1, 404]

4.2 Proportions for each covariate and standardized differences comparing opioid use disorder without *any prior* depression and opioid use disorder with *any prior* depression before and after weighting for all prior diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis-*Not including prior buprenorphine prescription*

	Crude (Unweighted)				Weighted (stabilized)[b]			
	OUD wo prior DEP (n=300)	OUD w prior DEP (n=217)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=300)	OUD w prior DEP (n=216)	Difference in proportions	Standardized differences
Age Category								
18-29	37.0	32.7	4.3	-0.090	35.8	37.5	1.7	0.036
30-39	36.3	36.3	0.0	0.021	36.3	35.7	0.6	-0.013
40-49	16.3	16.1	0.2	-0.006	16.1	16.1	0.0	0.001
50+	10.3	11.8	0.5	0.107	11.8	10.7	1.1	-0.034
Male sex	57.3	38.7	18.6	-0.379	48.9	48.5	0.4	-0.008
Non-Hispanic Ethnicity	99.0	97.7	1.3	-0.103	97.7	97.8	0.1	0.007
White race	99.3	99.5	0.2	0.027	99.5	99.6	0.1	0.016
Prior MH dx	37.0	79.7	42.7	0.960	55.3	56.6	1.3	0.030
Prior SU dx[a]	64.7	88.0	23.3	0.570	75.3	77.2	1.9	0.046
Prior Med dx[a]	31.0	47.9	16.9	0.351	38.1	39.0	0.9	0.018
Prior HIV/ Hep C dx[a]	9.0	11.5	2.5	0.083	11.3	12.0	0.7	0.025
Prior chronic pain dx[a]	20.3	30.9	10.6	0.243	25.8	26.3	0.5	0.012

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx

4.3 Proportions for each covariate and standardized differences comparing opioid use disorder without *past year* depression and opioid use disorder with *past year* depression before and after weighting for all past year diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis--*Not including past year buprenorphine prescription*

	Crude (Unweighted)				Weighted (stabilized)[b]			
	OUD wo past year DEP (n=300)	OUD w past year DEP (n=82)	Difference in proportions	Standardized differences	OUD wo past year DEP (n=298)	OUD w past year DEP (n=82)	Difference in proportions	Standardized differences
Age Category								
18-29	37.0	34.2	2.8	-0.059	34.9	39.7	4.8	0.101
30-39	36.3	39.0	2.7	0.055	38.8	39.4	0.6	0.012
40-49	16.3	15.9	0.4	-0.013	15.4	8.8	6.6	-0.179
50+	10.3	11.0	0.7	0.021	10.9	12.1	1.2	0.038
Male sex	57.3	42.7	14.6	-0.295	54.1	37.3	16.8	-0.337
Non-Hispanic Ethnicity	99.0	96.3	2.7	-0.176	98.5	98.0	0.5	-0.034
White race	99.3	100.0	0.7	0.116	100.0	100.0	0.0	0.000
Prior year MH dx[a]	15.0	73.2	58.2	1.439	28.2	34.3	6.1	0.153
Prior year SU dx[a]	27.3	69.5	42.2	0.927	37.8	43.0	5.2	0.114
Prior year Med dx[a]	13.0	39.0	26.0	0.618	19.6	23.6	4.0	0.095
Prior year HIV/ Hep C dx[a]	1.7	4.9	3.2	0.118	2.2	3.6	1.4	0.079
Prior year chronic pain dx[a]	6.7	23.2	16.5	0.474	9.8	10.8	1.0	0.029

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. within 1 year prior to first OUD dx date)

[b] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior year MI dx, prior year SUD dx, prior year Medical dx, prior year HIV or Hep C dx, prior year chronic pain dx

4.4 Recurrent events survival analysis hazard ratios with 95% confidence intervals (CI) for comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression (reference) and OUD with any prior/past year depression

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-g]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-g]
All prior depression[a]	251	1.86	0.85 [0.64, 1.12]	0.80 [0.59, 1.09]	110	0.82	1.01 [0.68, 1.51]	0.75 [0.47, 1.20]
Past year depression[b]	188	1.84	0.83 [0.52, 1.35]	0.84 [0.58, 1.22]	87	0.85	1.13 [0.77, 1.64]	1.09 [0.70, 1.69]

[a] Crude N=517; IPTW N=512

[b] Crude N=382; IPTW N=370

[c] Cox proportional hazards model: the ***Prentice, Williams and Peterson (PWP)*** was used to estimate crude and stabilized IPTW hazard ratios

[d] Stabilized IPTW for all prior depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

[e] All prior depression regression model adjusted for time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

[f] Stabilized IPTW for past year depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

[g] Past year regression model adjusted for sex, time since first OUD diagnosis, and time since first buprenorphine prescription (if occurred prior)

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-g]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-g]
All prior depression[a]	251	1.86	1.23 [0.95, 1.59]	**1.51 [1.12, 2.04]**	110	0.82	1.20 [0.81, 1.78]	1.50 [0.93, 2.42]
Past year depression[b]	188	1.84	1.36 [0.98, 1.90]	**2.13 [1.42 3.19]**	87	0.85	1.59 [0.98, 2.59]	**2.01 [1.05, 3.83]**

[a] Crude N=517; IPTW N=512

[b] Crude N=382; IPTW N=370

[c] Cox regression survival analysis for recurrent events, accounting for ***clustering*** of multiple encounters per person used to estimate crude and stabilized IPTW hazard ratios

[d] Stabilized IPTW for all prior depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

[e] All prior depression regression model adjusted for time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

[f] Stabilized IPTW for past year depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

[g] Past year regression model adjusted for sex, time since first OUD diagnosis, and time since first buprenorphine prescription (if occurred prior)

4.5 Recurrent events survival analysis hazard ratios with 95% confidence intervals (CI) for comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression (reference) and OUD with any prior/past year depression—*not adjusting for time since OUD diagnosis or time since first buprenorphine prescription (if occurred prior)*

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-e]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-e]
All prior depression[a]	251	1.86	0.85 [0.64, 1.12]	0.53 [0.26, 1.08]	110	0.82	1.01 [0.68, 1.51]	0.78 [0.48, 1.28]
Past year depression[b]	188	1.84	0.83 [0.52, 1.35]	0.76 [0.47, 1.23]	87	0.85	1.13 [0.77, 1.64]	1.09 [0.71, 1.68]

[a] Crude N=517; IPTW N=512

[b] Crude N=382; IPTW N=370

[c] Cox proportional hazards model: the ***Prentice, Williams and Peterson (PWP)*** used to estimate crude and stabilized IPTW hazard ratios

[d] All prior depression stabilized IPTW included the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

[e] Past year depression stabilized IPTW included the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-e]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI][c]	IPTW adjusted Hazard Ratio [95% CI][c-e]
All prior depression[a]	251	1.86	1.23 [0.95, 1.59]	**1.50 [1.12, 2.03]**	110	0.82	1.20 [0.81, 1.78]	1.44 [0.89, 2.35]
Past year depression[b]	188	1.84	1.36 [0.98, 1.90]	**2.22 [1.47, 3.34]**	87	0.85	1.59 [0.98, 2.59]	**2.13 [1.13, 4.03]**

[a] Crude N=517; IPTW N=512

[b] Crude N=382; IPTW N=370

[c] Cox regression survival analysis for recurrent events, accounting for ***clustering*** of multiple encounters per person used to estimate crude and stabilized IPTW hazard ratios

[d] All prior depression stabilized IPTW included the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

[e] Past year depression stabilized IPTW included the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

4.6 First event survival analysis hazard ratios with 95% confidence intervals (CI) for comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression (reference) and OUD with any prior/past year depression—*not adjusting for time since OUD diagnosis or time since first buprenorphine prescription (if occurred prior)*

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][c,d]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][c,d]
All prior depression[a]	189	1.95	1.25 [0.94, 1.66]	**1.58 [1.14, 2.17]**	95	0.85	1.22 [0.81, 1.82]	**1.57 [0.97, 2.54]**
Past year depression[b]	139	1.90	1.37 [0.95, 2.00]	**1.91 [1.24, 2.94]**	73	0.87	**1.60 [0.97 2.65]**	**2.23 [1.20, 4.13]**

[a] Crude N=517: IPTW N=512

[b] Crude N=382; IPTW N=370

[c] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

[d] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

4.7 Buprenorphine retention and discontinuation comparing adults with OUD without prior depression and those with OUD any prior/past year depression excluding patients with any extended release formulations (Any prior depression: N=517, Past year depression: N=382)-- *not adjusting for time since OUD diagnosis, time since first buprenorphine prescription (if occurred prior), or time between first and last MAT clinic date*

	180 day retention[a]		Any discontinuation[b]	
	OR [95% CI]	Weighted OR [95% CI][c]	OR [95% CI]	Weighted OR [95% CI][d]
Any prior depression	1.19 [0.82, 1.72]	0.92 [0.58, 1.47]	**1.77 [1.13, 2.76]**	**2.35 [1.37, 4.04]**
Past year depression	1.69 [0.99, 2.88]	1.38 [0.63, 3.01][e]	**2.02 [1.10, 3.71]**	**2.83 [1.26, 6.34][e]**

[a] Within first year of first buprenorphine prescription
[b] Defined as 30 or more days between buprenorphine prescriptions
[c] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx
[d] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx
[e] Doubly robust model including sex in propensity score weight and adjusted regression model

4.8 Buprenorphine retention and discontinuation comparing adults with OUD without prior depression and those with OUD any prior/past year depression, *excluding patients with first buprenorphine date after first date of medication-based treatment clinic visit* (Any prior depression: N=487, Past year depression: N=360)

	180 day retention[a]		Any discontinuation[b]	
	OR [95% CI]	Weighted OR [95% CI][c,d]	OR [95% CI]	Weighted OR [95% CI][d,e]
Any prior depression	1.16 [0.80, 1.68]	0.59 [0.33, 1.06]	1.28 [0.80, 2.03]	1.73 [0.96, 3.13]
Past year depression	1.59 [0.96, 2.65]	0.41 [0.16, 1.05][f]	**1.93 [1.06, 3.48]**	2.34 [0.96, 5.71][f]

[a] Continuous (no gaps or discontinuation)
[b] Defined as 30 or more days between buprenorphine prescriptions (60 days for extended release formulations)
[c] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx
[d] Regression model adjusted for time since first OUD diagnosis, time since first buprenorphine prescription (if occurred prior) and time between first and last medication-based clinic visit
[e] Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx
[f] Doubly robust model including sex, age categories 19-29 and 40-49, past year mental health disorder and past year substance use disorder in propensity score weight and adjusted regression model

4.9 Hazard ratios with 95% confidence intervals (CI) for comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression (reference) and OUD with any prior/past year depression, *excluding patients with first buprenorphine date after first date of medication-based treatment clinic visit*

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][c-f]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][c-f]
All prior depression[a]	176	1.96	1.19 [0.89, 1.60]	**1.45 [1.03, 2.05]**	88	0.85	1.19 [0.78, 1.80]	1.64 [0.99, 2.70]
Past year depression[b]	131	1.93	1.32 [0.90, 1.95]	**1.64 [1.03, 2.62]**	68	0.87	1.57 [0.93, 2.65]	1.85 [0.96, 3.54]

[a] Crude N=487; IPTW N=480

[b] Crude N=360; IPTW N=348

[c] Stabilized IPTW for all prior depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

[d] Stabilized IPTW for past year depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

[e] For all prior depression, regression model adjusted for time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

[f] For past year depression, regression model adjusted for sex, age categories 19-29 and 40-49, past year mental health disorder and past year substance use disorder, time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

4.10 Proportions for each covariate and standardized differences comparing opioid use disorder without *any prior* depression and opioid use disorder with *any prior* depression before and after weighting for all prior diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis and *no extended release buprenorphine prescriptions*

	Crude (Unweighted)				Weighted (stabilized)[b]			
	OUD wo prior DEP (n=286)	OUD w prior DEP (n=194)	Difference in proportions	Standardized differences	OUD wo prior DEP (n=286)	OUD w prior DEP (n=193)	Difference in proportions	Standardized differences
Age Category								
18-29	37.1	30.9	6.2	-0.130	35.0	37.4	2.4	0.052
30-39	35.3	36.6	1.3	0.027	36.3	34.4	1.9	-0.039
40-49	16.8	17.5	0.7	0.020	16.5	16.7	0.2	0.005
50+	10.8	14.9	4.1	0.123	12.2	11.5	0.7	-0.022
Male sex	58.4	39.7	18.7	-0.380	50.9	49.6	1.3	-0.026
Non-Hispanic Ethnicity	99.0	97.4	1.6	-0.115	97.4	97.5	0.1	0.004
White race	99.3	99.5	0.2	0.024	99.4	99.6	0.2	0.015
Prior MH dx	35.7	78.9	43.2	0.969	53.7	55.3	1.6	0.037
Prior SU dx[a]	64.7	88.1	23.4	0.574	75.1	76.0	0.9	0.022
Prior Med dx[a]	31.8	46.4	14.6	0.301	37.0	37.7	0.7	0.014
Prior HIV/ Hep C dx[a]	9.4	11.3	1.9	0.062	11.4	11.9	0.5	0.016
Prior chronic pain dx[a]	20.3	32.0	11.7	0.268	25.6	26.4	0.8	0.019
Prior buprenorphine rx[a]	3.5	11.9	8.4	0.317	7.1	7.5	0.4	0.016

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. Prior to first OUD dx date)

[b] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

4.11 Proportions for each covariate and standardized differences comparing opioid use disorder without *prior* depression and opioid use disorder with *past year* depression before and after weighting for all past year diagnoses limited to patients with at least a year of observation prior to first opioid use disorder diagnosis and *no extended release buprenorphine prescriptions*

	Crude (Unweighted)				Weighted (stabilized)[b]			
	OUD wo past year DEP (n=286)	OUD w past year DEP (n=69)	Difference in proportions	Standardized differences	OUD wo past year DEP (n=284)	OUD w past year DEP (n=69)	Difference in proportions	Standardized differences
Age Category								
18-29	37.1	30.4	6.6	-0.140	34.9	41.2	6.3	0.134
30-39	35.3	39.1	3.8	0.079	37.2	32.8	4.4	-0.092
40-49	16.8	17.4	0.6	0.016	15.8	9.6	6.2	-0.164
50+	10.8	13.0	2.2	0.068	12.1	16.4	4.3	0.132
Male sex	58.4	44.9	13.5	-0.271	55.8	30.0	25.8	-0.519
Non-Hispanic Ethnicity	99.0	95.7	3.3	-0.203	98.4	97.4	1.0	-0.066
White race	99.3	100.0	0.7	0.118	100.0	100.0	0.0	0.000
Prior year MH dx[a]	14.0	75.4	61.4	1.561	26.1	35.8	9.7	0.245
Prior year SU dx[a]	26.6	72.5	45.9	1.028	36.8	47.6	10.8	0.242
Prior year Med dx[a]	13.6	37.7	24.1	0.570	19.2	26.1	6.9	0.165
Prior year HIV/ Hep C dx[a]	1.7	5.8	4.1	0.212	2.8	5.0	2.2	0.116
Prior year chronic pain dx[a]	6.3	26.1	19.8	0.555	10.0	12.6	2.6	0.074
Prior year buprenorphine rx[a]	0.7	2.9	2.2	0.165	1.4	1.7	0.3	0.026

[a] The definition of all of these DO NOT include the day of OUD dx (e.g. within 1 year prior to first OUD dx date)

[b] Stabilized inverse probability treatment weights; Includes the following covariates: age, race, ethnicity, sex, prior year MI dx, prior year SUD dx, prior year Medical dx, prior year HIV or Hep C dx, prior year chronic pain dx, prior year buprenorphine prescription (ordered)

4.12 Buprenorphine retention and discontinuation comparing adults with OUD without prior depression and those with OUD any prior/past year depression, excluding patients with any extended release buprenorphine prescriptions (Any prior depression: N=480, Past year depression: N=355)

	180 day retention[a]		Any discontinuation[b]	
	OR [95% CI]	Weighted OR [95% CI][c,d]	OR [95% CI]	Weighted OR [95% CI][d,e]
Any prior depression	1.19 [0.37, 1.72]	0.60 [0.32, 1.11]	1.10 [0.67, 1.83]	1.71 [0.90, 3.25]
Past year depression	**1.80 [1.06, 3.05]**	0.60 [0.20, 1.83][f]	1.48 [0.76, 2.90]	1.45 [0.43, 4.86][f]

a Continuous (without gaps or discontinuation)

b Defined as 30 or more days between buprenorphine prescriptions (60 days for extended release formulations)

c Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx

d Regression model adjusted for time since first OUD diagnosis, time since first buprenorphine prescription (if occurred prior) and time between first and last medication-based clinic visit

e Stabilized IPTW; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx

f Doubly robust model including sex, age categories 19-29 and 40-49, past year mental health disorder and past year substance use disorder in propensity score weight and adjusted regression model

4.13 Hazard ratios with 95% confidence intervals (CI) for comparing incidence of treatment gaps and discontinuation between adults with OUD without prior depression (reference) and OUD with any prior/past year depression, excluding patients with any extended release buprenorphine prescriptions

	Gap or discontinuation				Discontinuation			
	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][c-f]	Number of events	Incidence rate per 1000 person-years	Crude Hazard Ratio [95% CI]	IPTW adjusted Hazard Ratio [95% CI][c-f]
All prior depression[a]	164	1.78	1.24 [0.91, 1.68]	**1.57 [1.09, 2.26]**	73	0.68	1.05 [0.66, 1.67]	1.66 [0.95, 2.91]
Past year depression[b]	120	1.70	1.27 [0.84, 1.92]	1.64 [0.92, 2.94]	56	0.69	1.26 [0.68, 2.34]	1.75 [0.68, 4.51]

a Crude N=480; IPTW N=479

b Crude N=355; IPTW N=338

c Stabilized IPTW for all prior depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, prior MI dx, prior SUD dx, prior Medical dx, prior HIV or Hep C dx, prior chronic pain dx, prior buprenorphine prescription (ordered)

d Stabilized IPTW for past year depression; adjusted for the following covariates in the propensity score analysis: age, race, ethnicity, sex, past year MI dx, past year SUD dx, past year Medical dx, past year HIV or Hep C dx, past year chronic pain dx, past year buprenorphine prescription (ordered)

e For all prior depression, regression model adjusted for time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

f For past year depression, regression model adjusted for sex, age categories 19-29 and 40-49, past year mental health disorder and past year substance use disorder, time since first OUD diagnosis and time since first buprenorphine prescription (if occurred prior)

4.14 Life tables for A) any gap or discontinuation, B) Any discontinuation in the first six months of buprenorphine treatment, by depression status

A. Any gap or discontinuation

OUD only (no prior depression) (n=300)						
Month	**n**	**Gap/discontinuation**	**Lost**	**Survival**	**Standard error**	**95% confidence interval**
0	300	20	15	0.931	0.015	0.896, 0.955
1	265	17	17	0.870	0.020	0.825, 0.904
2	231	11	30	0.826	0.023	0.775, 0.866
3	190	7	17	0.794	0.025	0.739, 0.838
4	166	10	15	0.744	0.028	0.684, 0.794
5	141	8	18	0.699	0.031	0.634, 0.754
6	115	2	16	0.686	0.031	0.620, 0.742
OUD + any prior depression (n=217)						
Month	**n**	**Gap/discontinuation**	**Lost**	**Survival**	**Standard error**	**95% confidence interval**
0	217	23	12	0.891	0.022	0.841, 0.926
1	182	9	13	0.845	0.025	0.788, 0.888
2	160	11	14	0.785	0.029	0.720, 0.836
3	135	5	10	0.754	0.031	0.687, 0.809
4	120	3	9	0.735	0.032	0.665, 0.792
5	108	8	11	0.677	0.036	0.602, 0.742
6	89	9	3	0.608	0.039	0.527, 0.679
OUD + past year depression (n=82)						
Month	**n**	**Gap/discontinuation**	**Lost**	**Survival**	**Standard error**	**95% confidence interval**
0	82	11	3	0.863	0.038	0.767, 0.922
1	68	4	4	0.811	0.044	0.706, 0.882
2	60	6	2	0.729	0.051	0.614, 0.814
3	52	2	3	0.700	0.053	0.583, 0.790
4	47	0	2	0.700	0.053	0.583, 0.790
5	45	3	4	0.651	0.056	0.529, 0.748
6	38	5	1	0.564	0.061	0.437, 0.673

B. Any discontinuation

OUD only (no prior depression) (n=300)						
Month	**n**	**Gap/discontinuation**	**Lost**	**Survival**	**Standard error**	**95% confidence interval**
0	300	11	15	0.962	0.011	0.933, 0.979
1	274	13	18	0.915	0.017	0.876, 0.942
2	243	7	36	0.887	0.019	0.843, 0.919
3	200	4	19	0.868	0.021	0.821, 0.904
4	177	5	17	0.842	0.023	0.790, 0.882
5	155	3	21	0.825	0.025	0.770, 0.868
6	131	1	18	0.818	0.026	0.761, 0.863
OUD + any prior depression (n=217)						
Month	**n**	**Gap/discontinuation**	**Lost**	**Survival**	**Standard error**	**95% confidence interval**
0	217	15	12	0.929	0.018	0.885, 0.957
1	190	8	13	0.888	0.022	0.837, 0.924
2	169	4	17	0.866	0.024	0.811, 0.906
3	148	4	11	0.842	0.026	0.782, 0.886
4	133	1	12	0.835	0.027	0.775, 0.881
5	120	3	15	0.813	0.029	0.748, 0.863
6	102	4	4	0.781	0.032	0.710, 0.836
OUD + past year depression (n=82)						
Month	**n**	**Gap/discontinuation**	**Lost**	**Survival**	**Standard error**	**95% confidence interval**
0	82	8	3	0.901	0.033	0.811, 0.949
1	71	4	4	0.848	0.040	0.748, 0.911
2	63	3	3	0.807	0.045	0.700, 0.879
3	57	3	3	0.763	0.049	0.650, 0.844
4	51	0	2	0.763	0.049	0.650, 0.844
5	49	2	5	0.731	0.052	0.613, 0.818
6	42	2	1	0.695	0.055	0.573, 0.789

Chapter 5: Discussion and Implications

5.1 Summary of findings

For the first time since the early 1900s, life expectancy in the US declined three years in a row, from 2014 to 2017, with drug overdose and suicide deaths contributing greatly to this change.[126,127] The contemporary overdose epidemic has claimed the lives of over 750,000 people since 1999,[1] not accounting for morbidity associated with substance use disorders and the countless number of people impacted by the epidemic over the past 20 years and prior. It has been especially detrimental in particular states and regions in the US, including rural Pennsylvania where the data from this dissertation comes from. Factors that have played a significant role go beyond that of just over-prescribing, but include structural, social and person-level drivers that impact the availability of and use of opioids, and access to needed resources and services. While this dissertation does not dive into many of these factors, it does tackle the complex health needs that are often not addressed among persons with opioid use disorder, and substance use disorders, more broadly.

Psychiatric comorbidity and specifically depression is not only significant because as this dissertation found, the prevalence is as high as 50% among persons with OUD but also because of the potential role in the intersection of overdose and suicide.[128] Further, while we know psychiatric comorbidity can impact retention in substance use disorder treatment, many questions remain about the specific relationship between depression and opioid agonist treatment. Answering these questions can help with treatment planning for persons with co-occurring opioid use and depressive disorders.

This dissertation aimed to fill the gaps in our understanding of co-occurring opioid use and depressive disorders by exploring personal characteristics and health conditions associated with the comorbidity, as well as examining utilization of healthcare services and buprenorphine

treatment among individuals with this comorbidity. This was done using electronic health and prescription medication records which allows for the capacity to assess real-world utilization patterns across time.

Overall, the analyses in this dissertation found that persons with co-occurring opioid use and depressive disorders have complex health needs illustrated by other medical conditions and health risks including lifetime overdose and suicide ideation and/or attempt. Depression may also play a unique role in the increased risk of emergency department encounters related to substance use and/or mental health problems and can potentially impact continuity of buprenorphine treatment. The following sections summarize the findings from each analysis, acknowledge strengths and limitations of each, delineate remaining research questions and future directions for practice, and finally present key public health implications.

Aim 1 utilized electronic health records prior to the fall of 2019 to describe characteristics, health conditions and overall healthcare utilization of adults with opioid use disorder (OUD) in the Geisinger Health System, and compare differences between those with and without a lifetime co-occurring depressive disorder. This study found that 49% of the study sample with OUD also had a depression diagnosis in their EHR. There were also a number of differences between persons with and without a lifetime depression diagnosis. Persons with co-occurring depression were more likely to be female and more likely to have other comorbid medical conditions, including hypertension, diabetes, chronic obstructive pulmonary disease or asthma. Co-occurring depression was also associated with greater odds of mental health and substance use disorders, other than depression and opioid use disorder, as well as increased likelihood of experiencing an overdose or suicidal ideation and/or suicide attempt. In regard to healthcare utilization, persons with depression were more likely to have ever received an

antidepressant medication and had a greater number of outpatient and emergency department encounters in their EHR.

These findings reiterate what is known from previous studies including the association between depression and overdose as well as suicide. The findings also highlight other medical comorbidities that this population face, emphasizing the importance of addressing all health conditions through integrated care. Based on the greater number of emergency department visits among persons with co-occurring depression, we might suspect that this could be impacted by barriers to accessing preventative healthcare as well as the complex health needs of this population. In summary, other comorbidities and health risks need to be considered when developing treatment plans and providing healthcare services to persons with co-occurring opioid use disorder and depression.

Aim 2 of this dissertation also used EHR data for encounters that took place prior to the fall of 2019 to assess differences in the risk of emergency department visits and inpatient hospitalizations following a person's first OUD diagnosis among patients with and without a preceding depression diagnosis. Of all emergency department encounters in the follow-up period, 73.2% included a code associated with a mental health or substance use diagnosis. This was also the case for 28.5% of inpatient hospitalizations. Persons with OUD and any prior depression had increased hazard for emergency department encounters that involved a suicidal ideation or suicide attempt code, as well as substance use disorder codes, other than OUD. Past year depression was also associated with increased risk of emergency department visits with mental health diagnoses. No differences were observed for inpatient hospitalizations.

Findings from Aim 2 provide more evidence that co-occurring psychiatric disorders, specifically depression, are associated with increased utilization of emergency departments.

These results are particularly telling for emergency department visits that included codes related to mental health and substance use disorders, suggesting that symptoms of these conditions could have been driving factors for the need to go to the emergency department. Addressing unmet need for mental health treatment among persons with co-occurring depression and OUD could help to reduce the need to utilize the emergency department.

Aim 3 of this dissertation utilized buprenorphine prescriptions data ordered in 2018 and 2019 by a health provider in the Geisinger Health System for patients who initiated buprenorphine treatment for opioid use disorder. In these analyses, the aim was to assess if those with co-occurring depression had a different risk of discontinuation or gaps in buprenorphine treatment, as well as if there were distinctions in odds of 180-day retention. Among all patients in the study sample, 40% remained in buprenorphine treatment at 180 days. Results from the time to event analysis suggest that depression preceding OUD was associated with increased risk of a gap in and/or discontinuation of treatment. Those who had a depression diagnosis code within the year prior to OUD also had decreased odds of 180-day retention.

The results of Aim 3 further demonstrate the complexity of co-occurring opioid use and depressive disorders and its impact on opioid agonist treatment. While depressive symptoms may decrease because of antidepressant properties of buprenorphine, having a prior depression diagnosis negatively impacts treatment continuity among this sample receiving care at an outpatient treatment center. Therefore, assessing depressive symptoms and incorporating care could help to reduce gaps in buprenorphine treatment and increase length of care.

5.2 Strengths and limitations

There are a number of strengths and limitations of this dissertation that need to be acknowledged. First, the analyses included in the dissertation help to fill important gaps in the

literature, related to co-occurring opioid use and depressive disorders. Second, as states such as Pennsylvania that have been particularly impacted by the opioid crisis continue to work to find solutions and improve the health of those affected, this work can provide information to health systems like Geisinger to help understand how depression might impact utilization and treatment continuity. Further, implications for practice could include assessing and managing depressive symptoms as patients progress with buprenorphine treatment.

The use of electronic health records and prescription medication data from a large integrated health system is valuable to explore real-world patterns of healthcare utilization and treatment for opioid use disorder. By using these records, we can explore these outcomes at the patient-level and across time as people engage in the healthcare system. Further, a strength of Geisinger, in particular, is the integration of the outpatient substance use treatment clinic data with other primary and specialty care clinic data. The integration is made possible with patient consent; which allows for continuity of care across the system for these patients as well as allowing for work such as this dissertation to be conducted. Because of this, data from all specialties including outpatient substance use treatment is integrated into the electronic health record with patient consent; which allows for work such as this dissertation to be conducted. In addition to the strengths of the data, there are also notable strengths of the research methods implemented. Specifically, to help deal with overt biases that can exist with observational data, propensity score methods were implemented. Using time to event modeling also created the ability to assess how depression affects time to each outcome explored.

Despite the strengths of using electronic health and prescription medication records, a number of limitations of these data exist. First because these data come from a specific health system in Pennsylvania, healthcare utilization and buprenorphine treatment outcomes may not

directly translate to other health systems and treatment clinics in other states because of differences in system policies and protocols. Related to generalizability, while the distribution of demographic characteristics of the study population is similar to that of the distribution across Pennsylvania, the sample includes almost entirely non-Hispanic white patients receiving healthcare in rural areas which limits generalizability to more racially diverse and urban populations. Limitations related to measurement are also important to address. For each of the aims, diagnostic codes were utilized to define exposure groups and other covariates. These diagnosis codes rely on the consistency and accuracy of recordings by healthcare providers. However, because this population was recruited from an outpatient substance use treatment clinic, addiction specialists verified the OUD diagnosis. Because administrative data are not collected for research purposes, there also could have been unmeasured factors not included in the electronic health and prescription medication records. Additionally, available information is limited to what is included in the EHR and prescription medical records. This is influenced by patient interactions with a health care system as well as what types of services are provided within the system. Lastly, the data are observational and therefore causality could not be examined.

5.3 Future directions for research and practice

While this dissertation helps to fill important gaps in the existing literature, in many ways it generates more questions for future research and practice. These questions are separated into two sections below: 1) healthcare service integration; 2) treatment for opioid use disorder.

Healthcare service integration

As depicted in this dissertation, persons with co-occurring OUD and depression have other co-occurring health conditions and therefore would greatly benefit from integrated care.

While treatment systems for mental illness, substance use disorders and other medical care have historically been independent,[129] integrative care models exist to reduce barriers associated with separate care and address the complex health needs by creating an integrated treatment plan that addresses all health conditions.[130] Health systems like Geisinger may be well positioned to ensure the implementation of integrated care. Future research should examine effects of integrated care on emergency department use and inpatient hospitalizations for substance use and mental health related conditions.

Additionally, results indicate that persons with co-occurring depression had an increased risk of utilizing the emergency department. In light of the opioid epidemic, there is increased attention on the role of emergency departments in reducing harms associated with opioid use and preventing overdose death. A number of emergency department protocols and interventions exist, including distributing naloxone, the use of peer navigators, initiating buprenorphine treatment, and linkage to other needed care.[131,132] Integrated health systems, like Geisinger should utilize these emergency department interventions and ensure linkage to and coordination with outpatient treatment clinics to create more continuity of care and remove barriers to needed treatment and medical care.

Treatment for opioid use disorder

This dissertation includes adults who have accessed healthcare services and initiated buprenorphine treatment within the Geisinger Health System. However, less than 20% of persons with an opioid use disorder receive any type of treatment for OUD[133] and among those who receive treatment, less than 30% receive opioid agonist medications as part of their treatment plan.[113] Persons who have comorbid depression also face unique barriers to accessing treatment for their mental health and substance use disorders.[23] More research is needed to understand

barriers specific to opioid agonist treatment among this population, as well as the potential impact of co-occurring depression on likelihood of initiating treatment that includes medication to treat OUD. Additionally, while the use of buprenorphine to treat OUD has increased in recent years,[35] it is not clear if this is the case among persons with co-occurring depression.

Lastly, more research is needed to investigate and improve treatment for OUD involving medications for persons with co-occurring depression. Because of the antidepressant properties of buprenorphine,[124,125] the associations that exist for depression and buprenorphine treatment continuity and retention may not be generalizable to the two other medications used to treat OUD- methadone and naltrexone. While all act through the endogenous opioid system, pharmacodynamics differ for these medications.

Significant for the association with depression, buprenorphine is a partial agonist at the mu receptor and an antagonist at the kappa receptor. Mu receptors are responsible for euphoric and analgesic effects, whereas kappa receptors antagonize mu activity and produce dysphoria, as well as some analgesic effects. Buprenorphine's kappa antagonism is what is argued to have the antidepressant effects.[58,125] While naltrexone also has kappa receptor antagonism properties, its affinity for kappa receptors is lower than it is for mu receptors. Naltrexone's ability to counteract increased activity at the kappa system is also thought to be weaker, therefore having less effect on mood symptoms.[59] In addition to the pharmacodynamics, processes for receiving and administering methadone, buprenorphine and naltrexone differ.

Naltrexone and buprenorphine treatment are typically administered through outpatient medical facilities, whereas methadone is administered at opioid treatment programs. Barriers related to stigma, dosing and prescribing restrictions are also prevelant.[44] Differences in retention and adherence also exist, particularly for naltrexone which requires patients to be abstinent from

opioids for one week prior to induction.[109] Future research should continue to explore the effects of buprenorphine on changes in depressive symptoms and how these changes might impact buprenorphine treatment continuity, retention and opioid-related outcomes. More evidence is needed to understand if persons with depression respond differently to treatment with methadone, as well as explore the impact of differences in administration and treatment protocols on treatment initiation and course among those with co-occurring depression. This should also be considered in practice when developing treatment plans to best address the needs to each patient.

5.4 Implications for public health

This dissertation highlights a number of public health implications. First, the studies highlight the need for engagement at different system levels to increase investment to expand treatment and healthcare services for persons with opioid use and depressive disorders. Removing barriers to use of medications to treat opioid use disorder, as well as to other medical and mental health care is imperative. This necessitates changes to regulatory barriers as well as increasing funding for treatment.[134] The integration of care is a particular need for the population of focus in this dissertation. Integrated treatment models require buy-in from health systems and healthcare providers to ensure that barriers are removed and that patients are getting the individualized care they need. Promising approaches exist, including Medicaid health homes[135] and the "hub-and-spoke" model,[136] but more action is needed to expand and ensure sustainability. Data surveillance and linkage is another public health priority. Collaboration across sectors, including researchers, policy makers and health system leadership is important to create and/or improve data collection and availability to identify risk factors, health outcomes, and access to and utilization of needed services. Finally, stigma against persons with substance use and mental health disorders remains a significant barrier. Stigma impedes access to and

utilization of evidence-based services both at the system and provider levels, and negatively impacts support for public health oriented policies related to opioid use.[137] Persons with co-occurring disorders are at particular risk for being impacted by stigma. Ongoing efforts to create policies and practices to eliminate stigma toward persons with substance use and mental health disorders should continue to be a focus as we implement strategies to address the ongoing opioid crisis in the US and work to improve health and well-being of persons with co-occurring opioid use and depressive disorders.

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101. Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. *Int J Epidemiol*. 2015;44(1):324-333. doi:10.1093/ije/dyu222

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104. Kariisa M. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential — United States, 2003–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68. doi:10.15585/mmwr.mm6817a3

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134. Saloner B, McGinty EE, Beletsky L, et al. A public health strategy for the opioid crisis. *Public Health Rep*. 2018;133(1_suppl):24S–34S.

135. McClellan C, Maclean JC, Saloner B, McGinty EE, Pesko MF. Integrated care models and behavioral health care utilization: Quasi-experimental evidence from Medicaid health homes. *Health Econ*. n/a(n/a). doi:10.1002/hec.4027

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137. Kennedy-Hendricks A, Barry CL, Gollust SE, Ensminger ME, Chisolm MS, McGinty EE. Social Stigma Toward Persons With Prescription Opioid Use Disorder: Associations With Public Support for Punitive and Public Health–Oriented Policies. *Psychiatr Serv*. 2017;68(5):462-469. doi:10.1176/appi.ps.201600056

Curriculum Vitae

Kayla N. Tormohlen

PERSONAL DATA

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Baltimore, MD 21205
ktormoh1@jhu.edu

EDUCATION AND TRAINING

2020	PhD	Substance Use Epidemiology, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health Advisor: Dr. Ramin Mojtabai Dissertation: Role of depression in healthcare service utilization and opioid agonist treatment among persons with co-occurring opioid use and depressive disorders
2016	MPH	School-Wide, Johns Hopkins Bloomberg School of Public Health Advisor: Dr. Karin Tobin Capstone: Health of exotic dancers and the risk environment: A review of the literature
2013	BA	Psychology, University of Northern Colorado

PROFESSIONAL EXPERIENCE

2016-2020	NIDA T32 Drug Dependence Epidemiology Training Fellow Department of Mental Health Johns Hopkins Bloomberg School of Public Health
2016-2020	Graduate Research Assistant Lighthouse Studies at Peer Point Department of Health, Behavior and Society Johns Hopkins Bloomberg School of Public Health
2019	Support Staff Baltimore County Opioid Response Strategy Bloomberg American Health Initiative Johns Hopkins Bloomberg School of Public Health
2018-2019	Graduate Research Assistant Adolescent Opioid Use and Opportunities for Intervention in Baltimore Department of Mental Health Johns Hopkins Bloomberg School of Public Health

2013-2015 Faculty Research Assistant: Project Coordinator
Center for Addictions, Personality and Emotion Research
University of Maryland, College Park

PROFESSIONAL ACTIVITIES

Society Memberships

College on Problems of Drug Dependence, 2018- Present
Member-In-Training
Society for Prevention Research, 2018
Student Member
Research Society on Marijuana, 2018
Student Member

EDITORIAL ACTIVITIES

Peer Review Activities

American Journal of Preventive Medicine
Drug and Alcohol Dependence
Drugs: Education, Prevention & Policy

HONORS AND AWARDS

Honors

2018 Society for Prevention Research Abstract of Distinction
2016 NIDA Drug Dependence Epidemiology Pre-Doctoral Training Grant
2013 Summa Cum Laude, University of Northern Colorado
2010-2013 University of Northern Colorado Dean's List of Academic Distinction
2011-2012 College of Education and Behavioral Sciences Undergraduate Scholar
2011-2012 University of Northern Colorado Junior Honor Society

Awards

2020 Lucy Shum Memorial Scholarship
2019 NIDA Director's Travel Award
2019 Johns Hopkins Addiction and Overdose Workgroup Travel Award
2015 JHSPH Department of Mental Health Centennial Essay Contest Award

PUBLICATIONS

Journal Articles

1. Doran, K., Collado, A., Taylor, H., Felton, J. W., **Tormohlen, K. N.,** & Yi, R. (in press). Methods to optimize recruitment, participation, and retention among vulnerable individuals participating in a longitudinal clinical trial. *Research and Theory for Nursing Practice.*

2. **Tormohlen, K. N.,** Krawczyk, N., Feder, K.A., Riehm, K., Crum, R.M., & Mojtabai, R. (2020). Evaluating the role of Section 1115 waivers on Medicaid coverage and utilization of opioid agonist therapy among substance use treatment admissions. *Health Services Research, 55,* 232-238.

3. Pacek, L., Reboussin, B., Green, K., La Flair, L., Storr, C., Alvanzo, A., Mojtabai, R., Cullen, B., Young, A., **Tormohlen, K.,** Riehm, K., & Crum, R. (2019). Current tobacco use, nicotine dependence, and transitions across stages of alcohol involvement: A latent transition analysis approach. *International Journal of Methods in Psychiatric Research, e1789,* 1-10.

4. Riehm, K. E., Feder, K. A., **Tormohlen, K. N.,** Crum, R. M., Young, A. S., Green, K. M., Pacek, L. R., La Flair, L. N., & Mojtabai, R. (2019). Prospective associations between time spent using social media and internalizing and externalizing problems among U.S. youth. *JAMA Psychiatry*, 76(12), 1266-1273

5. Riehm, K. E., Young, A. S., Feder, K., Krawczyk, N., **Tormohlen, K.,** Pacek, L. R., Mojtabai, R., & Crum, R. M. (2019). Mental health problems and initiation of e-cigarette and combusted cigarette use among U.S. youth. *Pediatrics, 144* (1), e2018293, 1-9.

6. Schneider, K. E., **Tormohlen, K. N.,** Brooks-Russell, A., Johnson, R. M., & Thrul, J. (2019). Patterns of co-occurring modes of marijuana use among Colorado high school students. *Journal of Adolescent Health, 64*(6), 807-809.

7. Thrul, J., **Tormohlen, K.,** & Meacham, M. (2019). Social media for tobacco cessation intervention: A review of the literature. *Current Addiction Reports,* 1-13.

8. **Tormohlen, K. N.,** Schneider, K. E., Johnson, R. M., Ma, M., Levinson, A. H., & Brooks-Russell, A. (2019). Changes in prevalence of marijuana consumption modes among Colorado high school students from 2015 to 2017. *JAMA Pediatrics, 173*(10), 988-989.

9. **Tormohlen, K. N.,** Tobin, K. E., & Latkin, C. (2019). Sources of stress among adults with co-occurring drug use and depressive symptoms. *Journal of Urban Health, 96*(3), 379-389.

10. **Tormohlen, K. N.,** Tobin, K. E., Davey-Rothwell, M. A., & Latkin, C. (2019). Low overdose responding self-efficacy among adults who report lifetime opioid use. *Drug and Alcohol Dependence, 201,* 142-146.

11. Troung, C., Krawczyk, N., Dejman, M., Marshall-Shah, S., **Tormohlen, K.,** Agus, D., & Bass, J. (2019). Challenges on the road to recovery: Exploring attitudes and experiences of clients in a community-based buprenorphine program in Baltimore City. *Addictive Behaviors, 93*, 14-19.

12. Yi, R., Milhorn, H., Collado, A., **Tormohlen, K. N.,** & Bettis, J. (2019). Uncommitted commitment: Behavioral strategy to prevent preference reversals by smokers. *Perspectives on Behavior Science.*

13. Crum, R. M., Green, K. M., Stuart, E. A., La Flair, L. N., Kealhofer, M., Young, A. S., Krawczyk, N., **Tormohlen, K. N.,** Storr, C. L., Alvanzo, A. A., Mojtabai, R., Pacek, L. R., Cullen, B. A., & Reboussin, B. A. (2018). Transitions through stages of alcohol involvement: The potential role of mood disorders. *Drug and Alcohol Dependence, 189,* 116-124.

14. Mojtabai, R., Feder, K., Kealhofer, M., Krawczyk, N., Storr, C., **Tormohlen, K. N.,** Young, A., Olfson, M., & Crum, R. M. (2018). State variations in Medicaid coverage and the use of behavioral health services: Results from a national longitudinal study. *Journal of Substance Abuse Treatment, 89,* 79-86.

15. Tobin, K., Edwards, C., Flath, N., Lee, A., **Tormohlen, K.**, & Gaydos, C. A. (2018). Acceptability and feasibility of a peer mentor program to train young Black men who have sex with men to promote HIV and STI home-testing to their social network members. *AIDS Care, 30*(7), 896-902.

16. **Tormohlen, K. N.,** Brooks-Russell, A., Ma, M., Schneider, K. E., Levinson, A. H., & Johnson, R. M. (2018). Modes of marijuana consumption among Colorado high school students after the initiation of retail marijuana sales for adults. *Journal of Studies on Alcohol and Drugs, 80*(1), 46-55.

17. Feder, K., Mojtabai, R., Krawczyk, N., Young, A . S., Kealhofer, M., **Tormohlen, K. N.,** & Crum, R. M. (2017). Trends in insurance coverage and treatment among persons with opioid use disorders following the Affordable Care Act. *Drug and Alcohol Dependence, 179,* 271-274.

18. Footer, K. H., Silberzahn, B. E., **Tormohlen, K. N.,** & Sherman, S. G. (2016). Policing practices as a structural determinant for HIV among sex workers: A systematic review of empirical findings. *Journal of the International AIDS Society*, *19*(4Suppl 3).

19. Stuppy-Sullivan, A. M., **Tormohlen, K. N.,** & Yi, R. (2016). Exchanging the liquidity hypothesis: Delay discounting of money and self-relevant non-money rewards. *Behavioural Processes*, *122*, 16-20.

20. Phillips, K. T., Phillips, M. M., Lalonde, T. L., & **Tormohlen, K. N.** (2015). Marijuana craving and academic motivation among college students. *Addictive Behaviors, 7,* 42-47.

Practice-Related Reports

1. Working group staff. (2019). Addressing the opioid epidemic in Baltimore County: Recommendations for progress. Report submitted to the Baltimore County Executive.

http://resources.baltimorecountymd.gov/Documents/Executive/progressrecommendations.pdf

PRACTICE ACTIVITIES

Presentations to policy-makers and other stakeholders

1. **Tormohlen, K. N.,** Ahmad, J., Andrews, E., & Park A. (July, 2019). Presentation on opioid response recommendation drafts to expert working group and general public.

Research finding dissemination through media appearances and other communication venues (federal, state, and local)

1. Media interview with The Associated Press. https://apnews.com/eed897566bca4d71a17fca4721ee589f

2. Media interview with MedPage Today. https://www.medpagetoday.com/publichealthpolicy/publichealth/81428

Curriculum Vitae

Kayla N. Tormohlen

PART II

TEACHING

Classroom Instruction

2019	Opioid Epidemic Seminar (co-instructors: J. Ahmad and J. Sharfstein) Biden School of Public Policy and Administration University of Delaware

Guest Lectures

2020	Substance Use and Mental Health Disorder Comorbidity The Epidemiology of Substance Use and Related Disorders (R. Johnson and J. Thrul)
2019	Substance Use and Mental Health Disorder Comorbidity The Epidemiology of Substance Use and Related Disorders (R. Johnson)
2019	Treatment Episode Data Set Psychiatric Epidemiology (W. Eaton and H. Volk)

Teaching Assistant and Mentorship Positions

2016-2020	Student Coordinator MPH Social and Behavioral Sciences Concentration (J. Denison and R. Kennedy) Johns Hopkins Bloomberg School of Public Health
2018-2020	MPH Capstone Teaching Assistant (M. Diener-West) Johns Hopkins Bloomberg School of Public Health
2019	Lead Teaching Assistant The Opioid Crisis: Problem Solving Seminar (J. Sharfstein and S. Allen) Department of Health Policy and Management Johns Hopkins Bloomberg School of Public Health
2018/2019	Lead Teaching Assistant Introduction to Mental Health Services (R. Mojtabai) Department of Mental Health Johns Hopkins Bloomberg School of Public Health
2017	Lead Teaching Assistant Current Issues in Public Health (M. McGinty) Department of Health Policy and Management Johns Hopkins Bloomberg School of Public Health

2014-2015	First-Year Innovation & Research Experience Mentor Center for Addictions, Personality and Emotion Research University of Maryland, College Park
2013-2015	Undergraduate Research Assistant Supervisor and Mentor Center for Addictions, Personality and Emotion Research University of Maryland, College Park

PRESENTATIONS

Scientific Meetings

1. **Tormohlen, K. N.,** Dayton, L., Tobin, K. E., & Latkin, C. (2019, June). Engagement in opioid agonist therapy and drug use among network members. Poster presented at the 2019 annual meeting of The College on Problems of Drug Dependence, San Antonio, Texas.

2. Krawczyk, N., Dejman, M., Truong, C., Marshall-Shah, S., **Tormohlen, K.,** Agus, D., & Bass, J. (2018, June). Integrating buprenorphine into peer-support: A qualitative study exploring motivators for engagement and retention in a community-based opioid treatment program in Baltimore City. Poster presented at the 2018 annual meeting of The College on Problems of Drug Dependence, San Diego, California.

3. Schneider, K. E., **Tormohlen, K. N.,** Brooks-Russell, A., & Johnson, R. M. (2018, July). Patterns of co-occurring modes of marijuana use among Colorado high school students. Poster presented at the 2018 scientific meeting for the Research Society on Marijuana, Fort Collins, Colorado.

4. Tobin, K. E., **Tormohlen, K. N.,** & Latkin, C. (2018, November). Differences in HIV risk behaviors by sex partner type among a sample of Black MSM: An analysis of social network characteristics. Oral presentation at the 2nd North American Social Networks Conference, Washington DC.

5. **Tormohlen, K. N.,** Schneider, K. E., Johnson, R. M., & Brooks-Russell, A. (2018, July). Changes in prevalence of modes of marijuana consumption among Colorado high school students from 2015 to 2017. Poster presented at the 2018 scientific meeting for the Research Society on Marijuana, Fort Collins, Colorado.

6. **Tormohlen, K. N.,** Tobin, K. E., Davey-Rothwell, M. A., & Latkin, C. (2018, June). Factors associated with overdose response self-efficacy among adults who report lifetime opioid use. Poster presented at the 2018 annual meeting of The College on Problems of Drug Dependence, San Diego, California.

7. **Tormohlen, K. N.,** Brooks-Russell, A., Ming, M., Schneider, K. E., Levinson, A. H., & Johnson, R. M. (2018, May). Changes in modes of marijuana consumption among Colorado high school students after recreational marijuana legalization: Differences by

sex, race, and grade. Organized paper symposium at the 2018 Society for Prevention Research 26th Annual Meeting, Washington DC.

8. **Tormohlen, K. N**., Tobin, K. E., & Latkin, C. (2017, June). Sources of stress and their correlates among adults who use drugs. Oral presentation at the 2017 annual meeting of The College on Problems of Drug Dependence, Montreal, Canada.

9. Stuppy, A. M., **Tormohlen K. N.,** & Yi, R. (2015, May). Delay discounting for money and personalized non-money rewards. Symposium presentation at the Association for Behavior Analysis International annual convention, San Antonio, Texas

10. **Tormohlen, K. N.,** Matusiewicz, A. K., Tyson, A., & Yi, R. (2014, June). Using rate of delay discounting to predict preference reversals for cigarette smokers. Poster presented at the annual meeting of The College on Problems of Drug Dependence, San Juan, Puerto Rico.

11. Morgan, E. C., & **Tormohlen, K.** (2013, April). Two weeks in the life of a college age marijuana user: A study using EMA and content analysis. Poster presented at the Rocky Mountain Psychological Association Convention, Denver, Colorado.

12. Dykema, K. R., Phillips, M. M., Phillips, K. T., Morgan, E. C., Nowak, J. T., Machlev, M., **Tormohlen, K.,** & the Motivation and Addiction Research Group (2012, August). Ecological momentary assessment with college-age marijuana users: Feasibility of SMS texting. Poster presented at the annual meeting of the American Psychological Association, Orlando, Florida.

Invited Seminars

1. **Tormohlen, K. N.** (2020, March). Co-occurring opioid use and depressive disorders, and its impact on emergency department visits. Oral presentation at the American Psychopathological Association Pre-APPA Training Program Workshop, New York, New York.

2. **Tormohlen, K. N.** (2018, February). Modes of marijuana consumption among Colorado high school students. Oral presentation at the Johns Hopkins Bloomberg School of Public Health Department of Mental Health Seminar Series.